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Long-term Survival of Patients with Breast Cancer and Brain Metastases: 'The experience of the 2nd Oncology Department of Metropolitan Hospital and a brief review of the literature'

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Abstract: **Background:** Novel therapeutic approaches and new compounds during the last decade have prolonged survival of breast cancer patients with metastatic disease, resulting in higher incidence of central nervous system (CNS) metastases. Many of these patients live longer than expected.

Patients and methods: We reviewed breast cancer patients with brain metastases from our department, living longer than 1 year. Our purposes were to present patient and treatment characteristics and correlate them with disease outcome. Moreover, we aimed at reviewing the current literature.

Results: We detected 20 women with brain metastases from breast cancer, living longer than 1 year. The mean age was 41 years (range 22–61 years). One (5%) woman had luminal A breast cancer type, four (20%) patients had luminal B and HER2 negative, nine (45%) patients luminal B and HER2 positive, four (20%) patients HER2 enriched and two (10%) patients had triple-negative breast cancer. Most of them (70%) had infiltrating ductal histological type and grade 3. Moreover, the majority had known metastatic disease when brain metastases appeared. The most common sites of disease were lung, liver and bone. Median time from breast cancer diagnosis until the presence of CNS metastases was 44 months (range 6–204 months). The progression free survival (PFS) of the most chemotherapeutic schedules was according to the literature. However, PFS of some compounds exceeded all expectations. Median time of survival was 25 months (range 13–116 months). Ten patients are still alive, having achieved a median survival rate of 35 months (range 17–78 months).

Conclusion: The combination of surgery, radiotherapy, chemotherapy and anti HER2 treatments is at present the best way to extend the OS and improve the quality of life of breast cancer patients with brain metastases. Prognostic markers for assessing brain metastases are required. Application of prophylactic treatment for these patients is under consideration.

Keywords: *Breast cancer • Brain metastases • Long-term survival*

Introduction

Cerebral metastases are common during the evolution of breast cancer and it is well known that they are associated with poor prognosis. The incidence of CNS metastases increased during the last decade. This is attributed to the progress of medical imaging and to the application of new therapeutical approaches in advanced breast cancer, which increases the survival of patients [1].

In 1964, the median survival of patients with breast cancer and cerebral metastases without therapeutic intervention was 1 month [2]. The symptomatic treatment (dexamethasone) extended survival to 2 months. The patient who undergoes radiotherapy (RT) or surgery reaches 3–6 months, and if the patient is treated with the combination of RT, surgery and chemotherapy, lives 12–25 months [3].

The current treatment approach includes surgery, various techniques of RT, cytotoxic drugs and anti-HER2 treatments. One major problem is that only a few drugs pass the blood–brain barrier to control the metastatic brain cancer cells [4].

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Breast cancer is not a single entity but it includes different subtypes with a variety of prognosis. Similarly, metastatic breast cancer cells in brain have different behaviour: some patients with breast cancer and brain metastasis live longer than the others even though their tumour has the same molecular characteristics. Are there any common characteristics of these long-term survivors? Which biomarker(s) is/are responsible for this phenomenon? There are not a lot of clinical trials with patients with brain metastases and unfortunately, there are not a lot of preclinical data for this group, thus we do not have the answers to the above questions.

In this study, we retrospectively reviewed data from a non-selected population of 20 women, with metastatic breast cancer in brain, living longer than 1 year. These women were treated with multiple chemotherapeutic schedules, as applied in the everyday practice of our department. The aim of this study is to describe the characteristics of these patients who achieved long-term survival, their tumour characteristics and their therapeutic approach. Furthermore, we analysed these data in correlation with current literature.

Patients and methods

Twenty women, treated between October 2001 and March 2014 for CNS metastases of breast cancer, were enrolled in this study. We investigated their clinical and molecular parameters such as TNM, ER, PgR, and HER2 in the presence of breast cancer and their prognostic influence after the occurrence of CNS metastases. No additional eligibility criteria were applied.

All patients had baseline computed tomography or magnetic resonance imaging of the brain, chest and abdomen. Radiographic response and serum tumour markers were evaluated every 12 weeks or earlier if there was clinical evidence of progression. Response was assessed with Response Evaluation Criteria in Solid Tumors (RECIST).

The HER2 status was considered positive if the local institution reported 3+ staining intensity (on a scale of 0–3) by means of immunohistochemical analysis or 2+ staining intensity by means of immunohistochemical analysis with gene amplification on fluorescence *in situ* hybridisation.

Adverse events were graded using NCI common toxicity criteria version 3.0 at baseline and every course of therapy. Criteria for discontinuation from each chemotherapeutic line included severe drug-related toxicity, progressive disease or change in patient's condition that made further treatment inappropriate.

Results

Patients' characteristics

Twenty female patients with CNS metastatic breast cancer were enrolled in this study. Baseline characteristics of the population included in this study are presented in Table 1. The mean age of the 20 patients analysed was 41 years (range 22–61 years).

Thirteen (65%) of these women were premenopausal and seven (35%) postmenopausal at the time of diagnosis of breast cancer. Unfortunately, the menopausal status at the time of the presence of brain metastases is unknown.

Fourteen women (70%) diagnosed with hormone receptor positive breast cancer (oestrogen and progesterone receptors). Moreover, fourteen (70%) women were HER2 positive and six (30%) HER2 negative. One woman (5%) had luminal A breast cancer, four (20%) patients luminal B and HER2 negative, nine (45%) patients luminal B and HER2 positive, four (20%) patients HER2 enriched and two (10%) patients had triple-negative initial breast cancer. Most of them (70%) had infiltrating ductal histological type and grade 3.

In five women (25%), the initial diagnosis was metastatic breast cancer while the rest of them (75%) had primary breast cancer and received adjuvant chemotherapy. All patients presented with CNS metastases. Most of them had known metastatic disease when they developed brain metastases. Thirty percent of the study population had one site of metastases when CNS metastases were established, 30% two sites and 20% more than three sites. Moreover, four patients (20%) presented with brain metastases as a first-appeared metastatic lesion.

It is obvious that until the presence of CNS metastases, most of the patients were heavily treated for advanced breast cancer. The regimens before treatment for CNS metastases of breast cancer included taxanes (85%), trastuzumab (65%), anthracyclines (75%), cyclophosphamide (70%), fluorouracil (45%), methotrexate (35%), vinorelbine (20%), platinum (30%), lapatinib (15%) and mitomycin (5%).

All patients had measurable disease, according to RECIST criteria. Their performance status was 0 (35%), 1 (45%) or 2 (5%) according to Eastern Cooperative Oncology Group. Their cardiac ejection fraction was within the institutional normal range and their laboratory function was adequate.

The most common presenting symptoms were headache (25%), neurologic deficit (20%) and nausea/vomiting (15%), which are in agreement with the literature.

Table 1. Patients characteristics.

Characteristics	No of patients %
Age, years	
Median	41
Range	22–61
Menopausal status at diagnosis of breast cancer–no. (%)	13 (65%)
Premenopausal status	7 (35%)
Postmenopausal	
Estrogen receptor status–no. (%)	
Positive	14 (70%)
Negative	6 (30%)
Progesterone receptor status–no. (%)	
Positive	14 (70%)
Negative	6 (30%)
HER2 status–no. (%)	
Positive	14 (70%)
Negative	6 (30%)
Size of primary breast lesions–no. (%)	
<0.5 cm	2 (10%)
0.6–2 cm	6 (30%)
2.1–5 cm	8 (40%)
>5 cm	1 (5%)
Unknown	3 (15%)
Ki67%–no.%	
<14	3 (15%)
>14	11 (55%)
Unknown	6 (30%)
Axillary node status–no. (%)	
0	5 (25%)
1–4	6 (30%)
>4	8 (40%)
Unknown	1 (5%)
Grade–no. (%)	
II	5 (25%)
III	14 (70%)
Unknown	1 (5%)
Histological type–no. (%)	
Infiltrating ductal	14 (70%)
Lobular invasive	2 (10%)
Multifocal	3 (15%)
Undifferentiated	1 (5%)
Adjuvant chemotherapy–no. (%)	
Yes	14 (70%)
No	5 (25%)
Unknown	1 (5%)
ECOG performance status in the presence of CNS metastases–no. (%)	
0	7 (35%)
1	9 (45%)
2	3 (15%)
Unknown	1 (5%)
No. of sites of disease before the appearance of CNS metastases	
Median	2
Range	0–3
Sites of disease before the appearance of CNS metastases–no. (%)	
Lung or pleura	10 (50%)
Liver	10 (50%)
Bone	13 (65%)
Adrenal gland	1 (5%)
No of prior chemotherapy regimens (except adjuvant)–no. (%)	
0	7 (35%)
1	9 (45%)
2	1 (5%)
>=3	3 (15%)
Types of prior chemotherapy exposure–no. (%)	
Trastuzumab	13 (65%)
Taxane	17 (85%)
Anthracycline	15 (75%)
Cyclophosphamide	14 (70%)
Fluorouracil	9 (45%)
Vinorelbine	4 (20%)
Capecitabine	5 (25%)
Platinum	6 (30%)
Methotrexate	7 (35%)
Lapatinib	3 (15%)
Mitomycin C	1 (5%)
Symptoms at the time of diagnosis of CNS metastases–no. (%)	
Headache	5 (25%)
Neurologic deficit	4 (20%)
Nausea/vomiting	3 (15%)
Others	2 (10%)
None	6 (30%)
Unknown	2 (10%)
Period to present CNS metastases from the first diagnosis–months	
Median	44
Range	6–206
Surgery	
Yes	5 (25%)
No	15 (75%)
CNS radiation–no. (%)	
None	1 (5%)
WBRT only	9 (45%)
SRS only	2 (10%)
Cyber knife	1 (5%)
Both WBRT and Cyber knife	5 (25%)
Both WBRT and SRS	2 (10%)
Chemotherapy after CNS metastases	
Yes	20 (100%)
No	0
Overal survival–months–10/20 patients	
Median	25
Range	13–116

Median time from breast cancer diagnosis until the presence of CNS metastases was 44 months (range 6–209 months). Surgical removal of the solitary brain lesion was performed only in 5 (25%) patients; the rest of them had multiple lesions, which were beyond surgical management. Subsequently, all patients except one were treated with CNS irradiation (Table 1).

Response and survival

The chemotherapeutic regimens administered after the diagnosis of brain metastases are shown in Table 2. It is mentioned that most of our patients had already been treated for advanced breast cancer. Unfortunately, there are not specific guidelines for the chemotherapeutic treatment of CNS metastases. The criteria of choosing

Table 2. Chemotherapeutic schedule after the presence of CNS metastases.

Chemotherapeutic schedule	Number of patients	PFS
Lapatinib+capecitabine	11	5 months (range 3–25 months)
Trastuzumab+lapatinib	9	5 (2–44)
Trastuzumab+vinorelbine	6	6 (3–7)
Trastuzumab monotherapy	4	7 (2–29)
Trastuzumab+ paclitaxel	4	3 (1–3)
Trastuzumab+docetaxel	4	5 (2–15)
Trastuzumab+capecitabine	3	9 (4–13)
Hormonal therapy	3	9 (3–17)
Trastuzumab+mitomycin C+cisplatin	3	3 (2–7)
Trastuzumab+ hormonotherapy	2	2–6
Capecitabine monotherapy	2	2–15
Trastuzumab+liposomal doxorubicin	2	3–10
Bevacizumab+paclitaxel	2	2–8
Vinorelbine+cisplatin+trastuzumab	1	2
Vinorelbine+gemcitabine	1	4
Lapatinib+gemcitabine	1	7
Lapatinib monotherapy	1	3
Bevacizumab+cisplatin+cyclopho sphamide	1	3
Carboplatin+gemcitabine	1	4
Bevacizumab+capecitabine	1	43
Topotecan+bevacizumab	1	17
Trastuzumab+temozolamide	1	2
Temozolamide monotherapy	1	2
Trastuzumab+gemcitabine+vino relbine	1	20
Trastuzumab+carboplatin+gemc itabine	1	4
Trastuzumab+gemcitabine	1	2
Trastuzumab+cisplatin+mitomycin C	1	3
Cyclophosphamide+liposomal doxorubicin	1	3
Vinorelbine+carboplatin	1	1
Trastuzumab+cisplatin+gemcit abine	1	12
Trastuzumab+temozolamide+lipos omal doxorubicin	1	5
Docetaxel monotherapy	1	5

PFS: Progression free survival

each chemotherapeutic line were the primary breast cancer characteristics, the performance status, the remaining toxicity from prior treatments, response to previous chemotherapeutic lines and the preference of each patient.

Patients with HER2-positive primary breast cancer (13 among 20) were treated with trastuzumab or lapatinib plus the approved chemotherapeutic combination. All the schemes were according to European Society for Medical Oncology guidelines. Most of the treatments had an average median time to progression of 5 months. Some of them were extremely effective, such as trastuzumab plus lapatinib (administered for 44 months in one HER2-positive patient) and bevacizumab plus capecitabine (administered for 43 months in one woman with hormonal receptor positive, HER2-negative disease).

Ten out of 20 women died. Thus the median overall survival (OS) was estimated in 25 months (range 13–116 months). Ten patients are still alive with performance status 1 or 2.

Discussion and review of the literature

Cerebral metastases in patients with breast cancer are not rare. The combination of surgery, RT and chemotherapy at present the best way to extend the OS and to ameliorate the quality of life.

Cerebral metastases occur in 20–40% of cancer patients. The most frequent types of cancer that spread into the brain are lung, breast, melanoma and kidney cancers. A total of 10–16% of patients with breast cancer present with one or more cerebral metastases. In autopsies, the incidence is 30% [5].

Breast cancer cell immigrate to the CNS and install in cerebral hemisphere and cerebellum, cranial nerves, meninges, spinal cord or the eye [4, 6]. Indeed, the incidence of breast cancer metastases to the eye is estimated to be higher than any other primary cancer [7]. According to the literature, most of the patients present multiple intracerebral metastases (78%). Fourteen percent of patients with metastatic breast cancer disease present solitary brain metastases and 8% present leptomeningeal metastases [8]. Seventy to eighty percent of patients have more than three tumour lesions [4]. Leptomeningeal metastases have been associated with poor survival [9]. In our study population, only one patient presented leptomeningeal metastases and is still alive after 2 years of the diagnosis of metastases. The other nineteen patients were diagnosed with intracerebral metastases and none of them with metastasis to the eye.

Most of the patients have already known metastatic disease when CNS metastases appear. The overall risk

of CNS metastases as the initial site is only 1.3% [10]. In our study, five out of 20 women were diagnosed with metastatic disease from the beginning. Among them, four had metastatic lesions to lung and bone and one to lung, bone and brain. Four out of five of these women had HER2-overexpressing tumour, while the fifth had luminal A tumour and is still alive. Three out of five of these women are still alive and it seems that their OS will overcome the median OS of this population. This observation does not confirm the initial state that metastatic disease at presentation has a poor prognosis. There are unknown pathogenic mechanisms and maybe unknown biomarkers, which play central prognostic role in this stage.

The frequency of CNS metastases depends on the histological type of breast cancer and the molecular subtype [4]. The frequency of brain metastases is 2.2% for luminal A, 4.7% for luminal B, 7.9% for luminalB/HER2 positive, 14.3% for HER2 enriched (HER2 positive, hormonal receptor negative) and 10.9% for basal like type [11]. It is assumed that one-third of HER2 breast cancer patients will develop brain metastases [12]. Probably, this is due to the ability of HER2 breast cancer cells to metastasise through vessels into the brain and the inability of trastuzumab to pass the blood–brain barrier [4]. In our population, luminal B HER2-positive patients were 45%, while triple negative were 10%. HER2 positive were 14 out of 20 women, as it was expected.

The patients having greater risk of expanding their breast cancer cells into the brain seem to be young premenopausal women, who overexpress HER2, but not hormonal receptors. Moreover, these patients usually have ductal histological type, large size of the primary tumour, lung metastases, mutation of BRCA1, high grade, p53 positive [13, 14]. Indeed, patients whose breast cancer cells do not express hormonal receptors are four times more likely to develop brain metastases than those who do. The same risk seems to be in patients with lung metastases, as a first site of relapse [15]. Moreover, studies have shown that triple-negative patients developed early CNS metastases and have poor prognosis (median survival time 2.9–4 months) [16, 17]. Our patients' characteristics seem to agree with the literature remarks. For example, young age, large tumour size, ductal histology and HER2 overexpression were the main characteristics of our population.

The period between the first diagnosis of cancer and the presence of brain metastases is 2–3 years or 34 months, according to Di Stefano *et al.* [11, 18]. Of course, it depends on the specific characteristics of the tumour. In our study, the median time from breast cancer metastases until the presence of brain metastases was 44 months (range 6–206 months). This outcome was better than the outcome reported in literature (24–36 months), but we underline that our population is small. The observation of Bachmann *et al.* [19] that HER2-positive patients had longer survival after the presence of brain metastases than HER2-negative patients seems to be confirmed in our study. The median OS of our patients with HER2-positive tumour was 38 months (range 20–116 months), while that of HER2-negative patients was 17 months (range 13–25 months). Thus, HER2 seems to be an important prognostic factor for the outcome of breast cancer patients. However, a French study showed that this advantage originates from the control of systemic disease with anti- HER2 biologic therapies [20].

It is interesting that two of our patients presented with brain metastases 16 and 17 years after the first diagnosis. Both of them were luminal A, premenopausal at the time of primary breast cancer. Unfortunately, they did not fulfil the criteria for surgical resection and the chemotherapeutic treatment was based on the characteristics of the primary tumour. These patients are still alive.

In the presence of brain metastases, the most common symptoms are headache (16–48%), neurologic deficit (16–40%), nausea and vomiting (11%), seizures (23%), cognitive dysfunction (14%), cranial nerve dysfunction (10%), cerebellar symptoms (2%) and speech disturbances (2%) [19, 21]. When cancer cells are located in meninges, the most common symptoms are headache, cervical inflexibility, dysfunction of peripheral nerves and neurological deficits. The symptoms of intracranial pressure include headache, nausea, vomiting, and mental status changes [6]. We observed the same symptoms as they are mentioned in the literature (Table 1).

For diagnosis of CNS metastases, CT scan and MRI scan are used. Especially, MRI has a higher sensitivity than CT [6].

Treatment approach

As mentioned above, treatment approach includes symptomatic treatment, surgical excision of solitary metastasis, stereotactic radiosurgery (SRS) for small (<3 cm) lesions not amenable to surgery, whole-brain radiotherapy (WBRT) and chemotherapy [4].

Symptomatic treatment included corticosteroids with H_2-receptor antagonist for gastric protection and anticonvulsants, such as phenytoin, carbamazepine, and sodium valproate if seizures occur. Among corticosteroids, dexamethasone is preferable due to its penetration into the brain [4, 22]. Prophylactic

anticonvulsant treatment has to be considered in cases of brain metastases in the motor cortex or coexisting brain metastases and leptomeningeal metastasis [23].

The indications for surgery are the necessity of new histologic report, the accessibility of the lesion(s), the amelioration of an insufferable symptom and the good performance status of the patient [4]. The differential diagnosis of a brain lesion, besides breast metastases, includes glioma, abscess or meningioma. Unfortunately, imaging methods are not always diagnostic to making surgery necessary. Doctors should have in mind that meningioma has a higher rate in patients with breast cancer than in general population [24, 25]. As far as the management of single brain metastases is concerned, surgical resection is the treatment of choice [26]. In case of uncertain single brain lesion, observation with MRI is preferable [27].

In our population, only 5 of 22 patients were eligible for surgery resection of solitary brain tumour. The immunophenotype of metastasis was not different from the primary tumour. Three of these patients are still alive. The OS seems to overcome the median OS of patients with brain metastases (over 22 months).

The selection of surgery or SRS depends on the size and location of metastases and the presence or absence of pressure effects. If the lesion is less than 3 cm, SRS is preferable. If metastatic lesion is located in motor or speech cortex, surgery is not recommended [21]. SRS is associated with lower risks for haemorrhage, infection, tumour seeding and lower costs as it does not require hospitalisation. However, the advantage of surgery is the relief of mass effects, pathologic diagnosis and no risk of radiation necrosis [28].

The role of radiation is essential in the treatment approach of breast cancer patients with CNS metastases. Especially, WBRT is considered standard treatment for these patients as it may delay progression of neurologic deficits and restore function [29, 30]. Headache, nausea, vomiting, fatigue, reversible hair loss, scull erythema are the most common toxicities from WBRT. Dementia, ataxia and urinary incontinence presented in long-term patients who have been treated with WBRT [31]. In patients with good performance status who develop recurrent lesions with limited systemic disease, oncologist should consider repeat WBRT [32]. All of our patients received WBRT.

Concerning the role of chemotherapy in CNS metastases of breast cancer patients, this is a misty area. Unfortunately, there are not a lot of studies to compare the efficacy of drugs in patients with breast cancer and cerebral metastases, as brain metastasis is an excluded criterion. Numerous drugs have been administered with low efficacy. One mechanism of resistance is glycoprotein P. Glycoprotein P is expressed in endothelium of capillaries in blood–brain barrier and prevents chemotherapeutic drugs such as anthracyclines, taxanes and vinorelbine from crossing the barrier and entering the cerebral circulation in order to approach the metastatic tumour cells and kill them [4]. Moreover, patients with metastases in brain are heavily pre-treated and cancer cells become resistant to chemotherapeutic drugs. However, in metastatic breast cancer and in an irradiated brain, the barrier is more foible and these agents seem to have some efficacy. It seems that the best responses are from young patients who have not received a lot of cytotoxic drugs. Patients who receive temozolamide, capecitabine, topotecan, platins, CMF, CAF seem to be of benefit. As mentioned above, trastuzumab cannot cross the blood–brain barrier and appear in the cerebrospinal fluid [33]. However, lapatinib, an anti-HER2 small molecule tyrosine kinase inhibitor seems to have CNS antitumour activity and may have a role as a radiosensitiser [12, 34].

Patients included in clinical trials are highly selected in contrast to our population, which was heavily pre-treated. Moreover, studies for patients with brain metastases from breast cancer are not many, as this population is very diverse and its previous therapeutic lines are different. One serious limitation of our study is the small population.

Moreover, we treated our patients with a lot of different chemotherapeutic regimens, as it is shown in Table 2 according to their primary breast cancer profile, their performance status and their previous therapies. The estimated median OS in our study population was 25 months, which is similar to the literature [12–25 months (3)]. Ten patients are still alive with acceptable performance status.

The PFS with the combination of lapatinib plus capecitabine was 5 months (range 3–25 months), which is higher than the PFS (3.65 months) of Lin *et al*'s study [12]. Similar PFS was observed in lapatinib monotherapy: one patient was treated with lapatinib monotherapy and her PFS was estimated at 3 months, while Lin *et al.* estimated PFS among 247 patients at 2.4 months. It seems that lapatinib has a role in the treatment of brain metastases in HER2-positive women [35].

Nine women were treated with a combination of lapatinib and trastuzumab. Their PFS was 5 months (range 2–44 months). The estimated PFS of this combination for metastatic breast cancer is 12 months [36]. It is expected that this PFS might be lower when metastatic cells immigrate to brain, but it is interesting to study the characteristics of one patient who received this combination for 44 months. This was a young premenopausal woman at the time of initial diagnosis,

with grade 2, luminal B/HER2-positive breast cancer; 67 months later, she developed unresectable brain metastases.

Another interesting combination was bevacizumab plus capecitabine, administered in a young woman. This patient had grade 3, luminal A tumour and 10 months after the initial diagnosis, she developed a solitary brain mass, which was resected. After the resection, she received bevacizumab plus capecitabine for 43 months and is still alive with hormonal therapy. Miller *et al.* did not show improvement in PFS or OS in the randomised Phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated for metastatic breast cancer. However, one of the exclusion criteria was brain metastases [37]. We suggest that bevacizumab might have a role in HER2-negative patients with brain metastases.

Another interesting chemotherapeutic regimen is temozolamide, which adequately penetrates the blood–brain barrier [38]. However, in patients with metastatic breast cancer, temozolamide does not seem to have the desirable results [39]. In our study population, one young woman received three cycles of temozolamide with good tolerance. This patient had luminal B HER2-positive advanced breast cancer, she presented brain metastases 88 months after the initial diagnosis and had already received six chemotherapeutic lines for brain metastases. After the third cycle of temozolamide, she presented with progressive disease in brain and we changed the chemotherapy regimen as she remained in performance status 1. Temozolamide appears to be more effective in combination with cisplatin [40]. However, the study population in literature is not only limited but also heavily pre-treated. This chemotherapeutic agent remains in the arsenal of therapeutic choices for the treatment of brain metastases and it remains to find its exact role for control of this stage of cancer.

Unfortunately, there are no specific biomarkers to prevent or predict brain metastases in breast cancer. Last year, Okuda *et al.* analysed cancer stem-like cells from metastatic breast cell lines, which are highly metastatic to brain *in vitro*. They found that these cells poorly express microRNA-7, resulting in high expression of KLF4. These two potential biomarkers may become therapeutic targets for brain metastases of breast cancer [41]. Other studies confirm that microRNAs regulate tumour metastases and play an important role in the evolution of brain metastases [42]. Another potential biomarker is Src kinase, a family of non-receptor tyrosine kinase, its hyperactivation was found to promote brain metastases in a preclinical model of breast cancer and it seems to be another therapeutic target, especially in HER2-enriched breast cancer patients [43]. Circulating tumour cells (CTCs) seem to have a particular role in the manipulation of the progress of breast cancer disease. We estimate that the liquid biopsy and the protein signature by the CTCs will play an important role in individualised therapy decisions in the near future [44]. Other molecules are under investigation and some of them are very promising in preclinical models and we believe that the following years, we will have more weapons in our arsenal to treat women with breast cancer and brain metastases. At present, 21 clinical trials are ongoing in the United States, studying novel therapeutic approaches in patients with metastatic breast cancer [45].

It is indisputable that CNS metastases remain a major clinical problem. They provoke despair in patients and embarrassment in doctors. Prophylactic RT is not recommended in breast cancer, because it does not seem that it is effective, as it is for lung cancer. However, we have to identify the high-risk patients for CNS metastases. Prognostic biomarkers for brain metastases are the locks and subsequently, the effective prophylactic treatment for these patients in order to prevent the spread of breast cancer cells into the brain is the key. The better understanding of the biology of the breast cancer cells will give us the impregnable tools to prevent their entry in the brain.

Acronyms

CNS: Cerebral nervous system;
ECOG: Eastern Cooperative Oncology Group;
HER2: Human epidermal growth factor receptor 2;
ER: Estrogen receptor;
PgR: Progesterone receptor;
IHC: Immunohistochemistry;
FISH: Fluorescence *in situ* hybridisation;
WBRT: Whole-brain radiotherapy;
SRS: Stereotactic radiosurgery;
RECIST: Response Evaluation Criteria in Solid Tumor;
PFS: Progression free survival;
OS: Overall survival;
ESMO: European Society for Medical Oncology.

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