

Breast cancer and metastases of the central nervous system

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Summary

Introduction: While five-year survival in metastatic breast cancer improved during the last decades, the likelihood of metastases of the central nervous system (CNS) has risen equally, making breast cancer the second most common source of CNS metastases. **Purpose of investigation:** Though prognosis of CNS metastases is generally poor, the clinical courses differ depending on the patterns of the CNS and periphery metastases. Various treatment options for CNS metastases are established in daily practice. **Materials and Methods:** Current literature and guidelines were reviewed in order to determine the optimal treatment strategy for each meta-static situation. **Conclusion:** In case of singular CNS metastases, neurosurgical interventions are promising approaches, while multiple CNS metastases are usually treated by radiation therapy, which might be combined with systemic treatment. Localized chemotherapy is applied in cases of leptomeningeal spread and may be combined with systemic treatment if needed.

Key words: Metastatic breast cancer; Brain metastases; Central nervous system; CNS; Focal radiation; Whole brain radiation; Intrathecal chemotherapy.

Introduction

With an increasing number of patients with metastatic breast cancer who survive her disease five years or longer [1], there is a higher likelihood that the central nervous system (CNS) is affected [2-4]. Nowadays breast cancer is already the second most common originator of CNS metastases. According to autopsies, the CNS is affected in up to 40% of cases of breast cancer.

Risk factors

By retrospective analyses of cohorts, it was possible to evaluate some factors which are associated with a higher probability of the occurrence of CNS metastases. These include young age at initial diagnosis (< 50 years), HER-2 positivity, and high grading. Triple negative tumours (ER, PR-, and HER-2- negative) indicate an especially high risk, even more so if the patient is premenopausal at the time of initial diagnosis. Retrospective analyses indicate that not only is the likelihood of an occurrence of CNS metastases increased, but also that the course of the disease is especially unpropitious. Further risk factors might be the improved results of adjuvant therapies and the use of trastuzumab in the treatment of breast cancer. An overview of these factors is shown in Table 1 [5-16].

Clinical manifestation

The majority of metastases of the CNS occur metachronistically. In more than two-thirds of the cases, the metastases in the CNS will be diagnosed because of the neurological symptoms [17, 18]. However, these can vary, depending on the prevalence of parenchymatous brain metastases or meningeosis carcinomatosa. In the latter, localisation in the area of the cerebrum is different from that in the neuroaxis. Depending thereon, the symptoms can normally be assigned quite specifically.

There is a wide variety of symptoms of CNS metastases. Therefore, each neurological symptom should draw attention to the potential affect of the CNS. A progression of the symptoms can occur rapidly and is strongly co-determined by the manner in which the metastases develop. In contrast to CNS metastases of lung cancer or

Table 1. — Risk factors for the occurrence of CNS metastases.

Young age (< 50 years vs. ≥ 50 years)	<i>p</i> = 0.001
Negative estrogen receptor status	<i>p</i> = 0.001
Grade 3	<i>p</i> = 0.002
Overexpression of HER-1- and HER-2	<i>p</i> = 0.001
“Basal-like“ cell type	<i>p</i> = 0.001
High Ki-67 index (> 15%)	
Successful treatment with trastuzumab for extracerebral lesions	
Successful adjuvant chemotherapy	

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malignant melanoma, singular metastases occur more often in breast cancer. Symptoms often are headaches, impaired vision, nausea, and emesis. Furthermore, there can be seizures or psychotic states.

Diagnosis

In most cases the diagnosis has to be made clinically, especially in patients with preexisting extracranial metastases. However, it is mandatory to perform imaging procedures, in order to distinguish metastases from other malignant tumours or from benign diseases. The contrast enhanced MRI is of utmost importance in this matter. Most cases can also be detected by cranial CT scans; however, the contrast enhanced MRI is the most reliable technique [19, 20]. In case of suspected meningeosis carcinomatosa, the neuroaxis should be included in the examination. Furthermore, in circa 70% of all cases, lumbar puncture leads to a detection of tumor cells in the cerebrospinal fluid.

Prognosis

Generally speaking, the life expectancy of patients with CNS metastases is just a few months, especially in cases of a disseminated decay of the meninges. However, the overall prognosis is strongly determined by the extracerebral tumor load and the control thereof as well as the patient's age and general condition. The best prognosis lies with patients in a good general condition with a singular brain metastasis and no extracerebral decay. As compared to other tumour entities, breast cancer patients have the best prognosis. There are single reports of long-term survivals for up to several years.

Therapy

Singular metastases

In case of a singular metastasis, neurosurgical intervention is often the best option. For optimal results, it should be followed by radiation of the complete brain. In case of smaller metastases (< three cm) stereotactic radiosurgical intervention can also be applied. These procedures are advantageous if there is a maximum amount of four foci. As a further requirement, the extracerebral metastases should be stable, otherwise the exclusive use of conventional radiation therapy should be preferred. However, this can be combined with a radiosurgical boost in prognostically favourable cases as described above [21-30].

Multiple metastases

The standard treatment in multiple brain metastases is the percutaneous radiation of the complete cranium, in case of existence of a perifocal edema supported by medication with steroids in order to prevent a progress of neurological symptoms. Substantial (temporarily complete) improve-

ment of the symptoms can be achieved in case of headaches in 50-70%, pareses in 30-40%, and in cerebral dysfunction in 40-50%. Disseminated metastases are not an indication for surgery. Radiotherapy roughly speaking doubles the median survival time as compared to treatment with steroids only (three vs. five months) [31-36].

Within brain metastases, there are extended hypoxic areas which reduce the efficiency of radiation therapy. The combination of whole brain radiation with efaproxiral [37] leads to significantly improved survival data, as compared with radiation therapy only. Efaproxiral changes the configuration of the hemoglobin molecule which leads to enhanced oxygen saturation in the tissue.

Concerning the role of chemotherapy, there is only data available from smaller phase II-studies. A systematic treatment may be considered in individual cases when radiotherapeutic or surgical options have been exhausted. The choice of substance need not necessarily be determined by the former criteria of liquor penetrancy as the integrity of the blood-brain barrier can no longer be assumed after radiation therapy [38].

The latest example of the undoubted efficiency of systemically effective substances, including brain metastases, is lapatinib. However, the hitherto existing data were assessed in massively pre-treated patients with HER 2-positive breast cancer [39]. Current studies evaluate this tyrosine kinase inhibitor beside others in the primary treatment of CNS metastases, in combination with radiation or intrathecal chemotherapy [41].

Leptomeningeal metastases

In case of leptomeningeal metastasis, intrathecal chemotherapy is the treatment of first choice. With methotrexate and the liposomal cytarabine, there are two substances available. A randomized study could not demonstrate any significant differences between the two of them [42].

In particular cases, whole brain radiation or focal radiation therapy can make sense. However, the existing substantiating evidence is very little and is based on small retrospective cohort studies.

A treatment interval of 14 days with DepoCyte leads to a significant improvement in life quality as compared to an application frequency of two to three times per week with methotrexate. Furthermore, the latter should be applied via an intraventricular reservoir because of its short exposure time in the cerebral fluid interspaces. However, such neurosurgical interventions are associated with a complication rate of 20-30%. When using DepoCyte, it needs to be considered that the substance has no admission yet for the treatment of solid tumours.

Analogous to the situation with solid brain metastases, there can be an indication to harmonise the treatment of a meningeal dissemination and of simultaneous metastases outside the CNS since half the patients die of a systemic

progress [43].

At the same time, the significance of a systemic chemotherapy for meningeosis carcinomatosa in breast cancer remains unclear. However, there are indications that the small subarachnoidal lumps of meningeosis which occur frequently cannot be reached with intrathecal chemotherapy. Current studies are assessing the benefit of a combination of systemic and intrathecal therapy in patients with meningeosis carcinomatosa [40].

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