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Long term disease free survival in a young patient with hormone receptor positive breast cancer and oligometastatic disease in the brain

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Introduction

Breast cancer is second only to lung cancer as the leading cause of cancer brain metastasis. Brain metastasis usually occurs late in the natural history of breast cancer and often in the presence of extensive extracranial metastasis [1]. The CNS presents as the sole site of metastatic disease in about 17% of patients according to a recent Austrian study [2]. We present a case of a young, premenopausal woman with estrogen receptor (ER) positive breast cancer with brain-only metastatic disease who has been treated with ovarian suppression, anastrozole, whole brain radiation therapy (WBRT), surgical resection, and intracavitary chemotherapy and continues to do well 13 years after her initial diagnosis.

Case

Our patient with a family history of breast cancer was diagnosed with breast cancer in 2002, at age 21, after presenting with bloody right nipple discharge. She underwent right breast lumpectomy and pathology showed low-grade ductal carcinoma in situ (DCIS) with a microscopic focus of invasive ductal carcinoma (IDC) that measured <2mm. Margins were positive for DCIS. A month later, she underwent a right simple mastectomy and left prophylactic mastectomy with immediate reconstruction. There were residual foci of low-grade DCIS in the right breast and margins were free of tumor. The left breast was pathologically unremarkable. There is no information available about hormone receptor or HER2 status from that time.

In 2003 she presented with a tender right axillary mass. Ultrasound revealed a 1.5 cm lymph node and needle aspiration revealed metastatic carcinoma. She underwent right axillary lymph node dissection and 8 of 13 lymph nodes were positive for IDC, which was strongly ER positive, progesterone receptor (PR) negative and HER2 negative. Metastatic evaluation was negative for distant metastatic disease.

She received four cycles of adjuvant dose dense Adriamycin and Cytoxan, followed by 4 cycles of Taxol. This was followed by adjuvant radiation to the right chest wall, axilla,

supraclavicular fossa and internal mammary lymph nodes. She then began ovarian suppression with leuprolide and anti-estrogen therapy with anastrozole.

In 2004 she presented with nausea, vomiting, and headaches. MRI of her brain revealed a cerebellar and a frontal lobe lesion with radiographic appearance of metastases. She underwent craniotomy and resection of the cerebellar lesion, followed by WBRT. Pathology confirmed the diagnosis of metastatic adenocarcinoma consistent with her breast primary. Testing for ER, PgR and HER2 expression was not done. A month after completion of WBRT she underwent stereotactic radiosurgery (SRS) to the frontal lobe lesion.

In 2005 she was hospitalized for new-onset seizures. An MRI brain revealed a new ring-enhancing metastatic lesion in the frontal lobe. She underwent a craniotomy for resection of the new right frontal lobe lesion. Later that year, a follow up brain MRI revealed a new, asymptomatic, right parietal lesion, which was also surgically resected Pathology was consistent with metastatic invasive ductal carcinoma. Given her young age, she underwent germline *BRCA* sequencing, which revealed a *BRCA2* polymorphism with no deleterious mutation detected in either the *BRCA1* or *BRCA2* genes.

In December 2006, a follow up brain MRI was concerning for recurrence in the region the initial right parietal lobe lesion and she underwent craniotomy in January 2007 for resection followed by intracavitary carmustine wafer (Gliadel) placement. Serial brain MRI studies between February 2007 and April 2015 have showed no evidence of recurrence and body CT imaging has shown no evidence of extracranial metastasis.

She continued anastrozole and leuprolide from November 2002 through April 2014 at which point she discontinued therapy to become pregnant. She is currently 31 years old—13 years out from her initial diagnosis—and has had no lasting neurologic deficits, no more seizures and she continues to work and live an active lifestyle.

Discussion

An estimated 10–30% of all breast cancer patients will eventually develop brain metastases [3]. The incidence of brain metastases in breast cancer is increasing due the aging population, detection of subclinical disease, and better control of systemic disease. Breast cancer brain metastases are associated with significant morbidity and mortality with the shortest survival time compared with other sites of metastatic spread [4].

In patients with early stage breast cancer, the cumulative incidence rates of brain metastasis are highest in those with HER2 positive and triple negative breast cancer (TNBC) and lowest in ER positive disease [4, 5]. Several studies have shown that the outcomes in patients with breast cancer brain metastases also differ by tumor subtype. In a study of 205 patients with breast cancer and brain metastases (28% TNBC, 53% HER2 positive, 19% luminal type), the median survival from the onset of brain metastasis was 3.7 months in TNBC, 9 months for HER2 positive and 15 months for luminal type breast cancer. Median survival from brain metastases was improved in all subgroups with systemic treatment after WBRT, but was particularly improved in the luminal subgroup with an improvement in median survival from 3 months to 14 months with systemic therapy [6].

Another study of 140 patients with breast cancer and brain metastases found that 27 patients (19%) were alive at least 36 months following diagnosis of brain metastases, and 10 patients (7%) were alive at least 60 months after this diagnosis. Of these 27 patients with significant long term disease free survival, 77% had ER positive disease, 70% had PR positive disease, 44% had Her2 positive disease, and 74% had a solitary brain lesion [7].

Brain only metastatic breast cancer

This case suggests that the pathobiology of patients with brain only disease may be inherently different with distinct clinical outcomes. In 2012, Berghoff and colleagues evaluated a cohort of 222 patients with breast cancer and brain metastases (26% luminal, 47% Her2, 27% triple negative) at their institution. Of these, 38 patients (17%) had brain-only metastatic breast cancer (BO-MBC). The patients with BO-MBC had significantly longer median overall survival as compared to patients with extracranial metastases (11 months vs 6 months). Long term survival of > 3 years was also significantly more common in patients with brain only metastases (seen in 7/38 patients, 18%). Interestingly, no association with BO-MBS and breast cancer subtype was seen in this study [2].

Treatment of brain metastasis in breast cancer

Favorable prognostic factors for BO-MBC include Karnofsky performance status (KPS) >70%, younger age, fewer lesions (<5 in some studies but no consensus on this) and ER expression [2, 8]. WBRT remains a current standard of care [9]. SRS is another option for patients with solitary or oligometastatic CNS disease and has a local control rate of up to 90% [9].

WBRT and SRS have been used together with improved disease control rates and reduced local recurrence rates compared with SRS alone. However, the combination is associated with significantly more neurocognitive morbidity than SRS alone [9, 10]. A recent study suggested that for patients younger than age 50 years there may be a survival advantage for SRS alone, compared with WBRT and studies are ongoing to determine whether use of WBRT should be reserved for patients who have multiple brain metastases that are not amenable to SRS or resection [11]. Where possible SRS or neurosurgical resection (NS) should be considered.

Past studies have shown that repeat NS in select patients can result in neurologic improvement with minimal morbidity and mortality as reported here [12]. Local recurrence after resection can occur in up to 46% of cases [13]. WBRT can be used in the adjuvant setting and has been shown to reduce local recurrence and improve disease control elsewhere in the brain [11]. No overall survival benefit has been demonstrated with use of adjuvant WBRT so a thorough discussion of the risks and benefits is warranted.

More recently, investigators have considered the use of carmustine wafer placement for salvage treatment of brain metastases (not limited to breast cancer) that have recurred in spite of SRS or surgical resection. These wafers, under the brand name Gliadel, were approved by the FDA in 1996 for the treatment of malignant glioma, and more recent studies have evaluated their adjuvant use in the setting of secondary CNS malignancies. The wafers

deliver a high concentration of chemotherapy (carmustine/BCNU) locally, after being surgically placed at the site of disease recurrence. Early clinical and preclinical studies have supported the safety and tolerability of this therapy for patients with brain metastases and recent studies demonstrated that successful local control can be achieved in patients with brain metastasis from breast cancer, non-small cell and small cell lung cancer, GI cancers, thyroid cancer and melanoma [13, 14].

Conclusion

We present a case of a young, premenopausal woman with ER positive metastatic breast cancer to the brain who has had prolonged progression free disease survival after aggressive treatment to achieve local control and hormone suppression. After multiple successful local treatment modalities including SRS, WBRT, neurosurgery and carmustine wafers, she has no evidence of significant neurocognitive dysfunction. In the absence of consensus guidelines for the management of brain-only oligometastatic breast cancer, we emphasize the importance of a multidisciplinary and multimodality approach. A patient having a good performance status, absent or well controlled extracranial disease and few metastatic lesions in the brain should first consider aggressive local therapy with surgery or SRS. Adjuvant WBRT can be considered but, when used in conjunction with SRS, the risk of neurocognitive morbidity should be discussed. Use of carmustine wafers should be considered as a salvage option in patients with good performance status and stable systemic disease who have had disease progression after surgery or SRS.

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Clinical Practice Points

- Incidence of brain metastases in breast cancer by subtype
- Management of brain metastases in breast cancer
- Long term DFS is possible as seen in this case of a young woman with hormone receptor positive breast cancer and oligometastatic brain metastasis.