Complete Radiologic Response of Bulky Cerebral Metastases From Newly Diagnosed HER2-Positive Breast Cancer to Upfront Trastuzumab-Based Chemotherapy

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Abstract

The blood-brain barrier is traditionally regarded as an insurmountable obstacle to the effective drug therapy of brain metastases from solid tumors. Here we describe a striking case of complete radiologic response to chemotherapy, and propose that the critical success factors include the large tumor size, HER2-positivity, and concomitant use of trastuzumab.

Keywords: Cerebral metastasis; Blood-brain barrier; Cancer chemotherapy; Breast neoplasms

Introduction

Oncology practice guidelines teach that neither cytotoxic therapy nor large-molecule target-specific therapies are routinely useful in treating cerebral metastases [1, 2] unless these arise from exquisitely chemosensitive primary tumors such as lymphomas or germ-cell neoplasms [3]. To address this unmet need, cerebral metastasectomy and/or stereotactic radiotherapy have become standards of care for most solid tumor patients with intracranial and limited extracranial metastatic disease [4], reflecting perceptions of a blood-brain barrier (BBB) that hinders transmembrane passage of drug molecules larger than 400 Da [5].

In recent years this orthodoxy has been challenged on empirical and theoretical grounds [6], with one objection being that the BBB is disrupted by intracerebral deposits larger than 1 cm [7]. HER2-overexpressing breast cancers are relevant to this debate, given that they recur preferentially within the brain [8], presumably reflecting the rich supply of HER-stimulatory heregulin ligands (neuregulins) [9] within the metastatic ‘soil’ of the central nervous system [10]. Relevant to this debate, we report here the history of a 50-year-old woman who presented with aggressive metastatic HER2+ breast cancer that required immediate upfront systemic therapy.

Case Report

A 50-year-old female presented in July 2012 after noticing thickening in the lateral aspect of the right breast. Core biopsy confirmed a 20 mm hormone receptor-negative grade 2 invasive ductal carcinoma with high levels of HER2 by both immunohistochemistry and in-situ hybridization. The patient reported no symptoms of metastatic disease, including no headaches or focal symptoms. Examination demonstrated a palpable breast mass with matted axillary lymph nodes, and normal neurological status. PET/CT scan demonstrated FDG-avid metastases in the right breast, right axillary lymph nodes, and multiple bilateral pulmonary nodules; in addition, however, a large photopenic and hypoattenuating area was detected in the right frontal lobe. CT-guided biopsy of a pulmonary nodule confirmed adenocarcinoma. Brain MRI confirmed two frontal lobe lesions (Fig. 1) (upper panels), the largest 28 mm, with extensive surrounding oedema. Gamma-knife surgery was deemed unfeasible due, but this was deemed unfeasible due to the size of the two lesions. Treatment was commenced using dexamethasone for cerebral oedema and 3-weekly standard chemotherapy using docetaxel/carboplatin plus trastuzumab (Herceptin™; DCH) with pegfilgrastim support. Repeat CT scan prior to the second cycle of DCH revealed a partial response, while a repeat MRI after five cycles showed a complete response (Fig. 1). There was also a clinical remission of the breast mass, a radiologic complete remission of the axillary adenopathy, plus near-complete remission of the pulmonary metastases. The patient continues on trastuzumab.
Discussion

Complete responses of brain metastases to systemic therapies have been reported for kinase inhibitor therapy of lung cancer [11]; for cytotoxic chemotherapy of germ-cell tumors [12]; and in breast cancer, for hormonal therapy [13], concurrent chemoradiation plus lapatinib [14], and (for small brain secondaries only) oral capecitabine [15]. In addition, responses of leptomeningeal breast cancer have been reported using intrathecal trastuzumab [16]. Partial responses of intracerebral metastases have been reported in pre-treated patients receiving tamoxifen [17], trastuzumab-radiation [18], trastuzumab-cytotoxic combinations [19], and capecitabine-lapatinib [20]. These testimonials to drug efficacy suggest that the traditional notion of the blood-brain barrier may be declining in relevance to the management of brain metastasis.

Trastuzumab reportedly exhibits poor penetration into the brain [21], and is widely believed to be ineffective in controlling brain metastases in breast cancer patients [22]. Despite this, trastuzumab induces radiosensitization in the context of cerebral metastases [23], and patients with HER2-positive brain metastases who continue trastuzumab experience longer survival [24, 25]. In contrast, the anticipated efficacy of the small-molecule HER2 kinase inhibitor lapatinib as single-agent therapy for brain metastases has proven to be marginal [26]. Indeed, based on published reports, we can infer no inverse relationship between drug molecular weight (Table 1) and clinical efficacy of brain metastasis therapy in breast cancer patients.

In summary, just as there is growing enthusiasm for first-line use of HER2 inhibitors in lieu of chemotherapy for early breast cancer [27], so does the present case suggest that trastuzumab-based chemotherapy could come to displace surgery and/or radiation therapy in selected cases of HER2-positive bulky brain metastases. Accordingly, in this palliative context, we submit that chemonaive HER2-positive intracerebral disease should now join lymphomas and germ-cell tumors in the category of “highly chemosensitive tumors” [3].

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Disclosures

All authors declare no conflict of interest.
Authors’ Contributions

DB and VS collected and interpreted the clinical data, LE supervised the imaging studies and interpretation, DB and RJE conceived and wrote the paper, and all authors were involved in the revision and approval of the final manuscript.

Abbreviations

BBB: blood-brain barrier; FLAIR: fluid-attenuated image recovery.

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Table 1. Molecular Weights of Relevant Oncology Drugs

| Drug          | Reported efficacy in solid tumour cerebral metastases | MWt (Da) |
|---------------|-------------------------------------------------------|----------|
| Capecitabine  | +                                                     | 360      |
| Carboptatin   | +                                                     | 371      |
| Tamoxifen     | +                                                     | 372      |
| Megestrol acetate | +                                                 | 384      |
| Gefitinib     | +                                                     | 447      |
| Dxorubicin    | -                                                     | 580      |
| Etoposide     | +                                                     | 587      |
| Docetaxel     | -                                                     | 808      |
| Lapatinib     | +                                                     | 944      |
| Trastuzumab   | +                                                     | 148,000  |

The putative blood-brain barrier cut-off is 400 Da. MWt: molecular weight; Da: daltons.
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