Intrathecal trastuzumab: 46 months and no progression

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A 43-year-old woman who was BRCA1 and -2 negative presented initially in 2002, when she was 35 years old, with inflammatory breast carcinoma on the right side. She was 9 months post partum. A biopsy revealed that the tumor was estrogen-receptor (ER)/progesterone-receptor (PR) negative and HER2 (human epidermal growth factor receptor–2) positive. She received neoadjuvant chemotherapy with adriamycin plus docetaxel for 6 cycles, followed by right mastectomy and prophylactic left mastectomy. There was no residual disease in the breast. After mastectomy, the patient underwent CMF (cyclophosphamide, methotrexate, and fluorouracil) chemotherapy for 3 months, as well as radiation therapy to the chest wall. Adjuvant trastuzumab was started concurrently with the CMF chemotherapy, and was continued for 1 year.

In 2004, the patient presented with headache and was found to have parenchymal brain metastases. She received whole brain radiation therapy along with temozolomide. Trastuzumab was restarted and was continued through May 2007. At that time, the patient's MRI raised the possibility of leptomeningeal carcinomatosis development, even though she was asymptomatic and her subsequent lumbar puncture was negative. When lapatinib became available, the patient was switched from trastuzumab to the newer drug, based on the concern raised by the MRI and the recent evidence showing lapatinib's improved CNS (central nervous system) penetration.

I met the patient in January 2008 when she developed mental status changes along with severe headaches. Her work-up revealed stable parenchymal disease, but changes on the gadolinium-enhanced MRI were consistent with leptomeningeal involvement (Figure); the MRI revealed abnormality in the dura mater of the brain and surrounding the lower thoracic and upper lumbar regions of the spine. No other evidence of disease on full body radiologic imaging was apparent. Lumbar puncture revealed increased protein levels, decreased glucose, and positive tumor cells. Despite intrathecal methotrexate (9 doses over a 5-week period) plus 3 doses of intrathecal thiotepa, the patient's cytology did not clear and her symptoms worsened. She developed seizures, had persistent severe headaches, and developed leg weakness. Intrathecal trastuzumab (25 mg in 5 mL of preservative-free saline) was administered every other day, based on recent abstract data.[1-3] We noted an improvement in her mental status within the first 3 days.

At 23 days after the initiation of intrathecal trastuzumab, an Ommaya reservoir was placed without complication, and about 3 weeks after placement of the Ommaya, capecitabine and lapatinib were added to the existing regimen. Over the ensuing 3 months, all of her neurologic compromises abated including resolution of her weakness, headaches, and confusion.

At 6 months after her discharge, intravenous trastuzumab was added to the patient's regimen with the hope of limiting systemic progression. She has now been receiving intrathecal trastuzumab for 44 months.

At 14 months after she began this new combination regimen, one of her previously treated parenchymal lesions progressed and was treated with Gamma Knife radiation. At 36 months into this treatment, that same parenchymal lesion appeared to grow. The patient underwent a craniotomy to remove the lesion; pathology revealed radiation necrosis with no active carcinoma. Her CSF cytology remains clear and

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MRI abnormalities in the dura mater of the spine remain stable (Figure 1). The remainder of the imaging has been negative. Before surgery, she had no neurologic compromise; after surgery, she had transient neurologic compromise, which has all abated.

The patient remained on intrathecal trastuzumab (25 mg in 5 mL of preservative-free saline given weekly), intravenous trastuzumab (6 mg/kg every 21 days), lapatinib (1,000 mg/day), and capecitabine (850 mg/m^2 a day in twice-daily dosing). At month 44, the intrathecal trastuzumab dosage was changed to 25 mg every 14 days, and the intravenous trastuzumab was switched to 4 mg/kg every 14 days.

When this patient began treatment, there were only two published abstracts reporting the use and safety of intrathecal trastuzumab in patients with HER2-positive carcinomatosis.[1,2] Dissemination of cancer into the CNS is greater in patients with HER2-overexpressing cancers.[2]

Leptomeningeal carcinomatosis represents a rare complication of breast cancer that occurs in approximately 3.5% of patients.[3-5] Intrathecal treatments with methotrexate, thiotepa, or cytarabine are usually effective for only a short period of time.[6] Very few systemic chemotherapeutics cross the blood-brain barrier well enough to control disease.

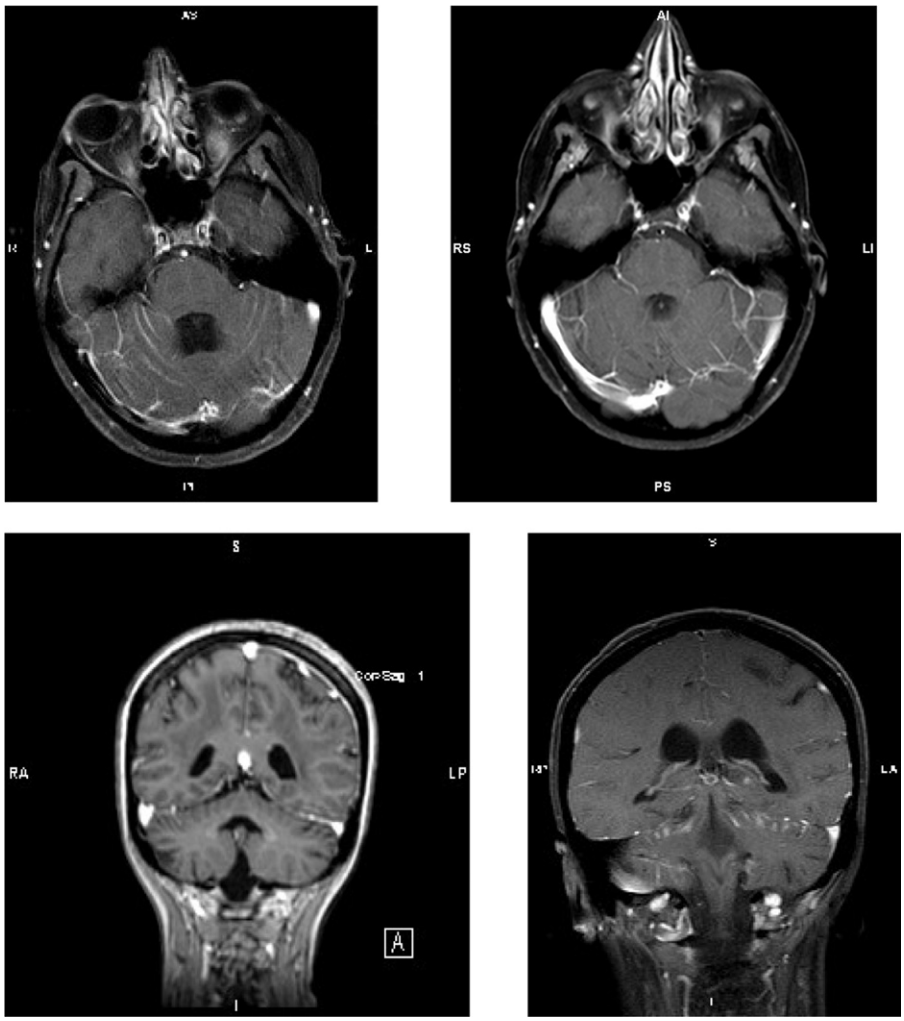

FIGURE In 2008, changes on the gadolinium-enhanced MRI (axial view, top left; coronal view, bottom left) were consistent with leptomeningeal involvement; the MRI revealed abnormality in the dura mater of the brain and surrounding the lower thoracic and upper lumbar regions of the spine. In 2011, after undergoing a craniotomy to remove a lesion, pathology revealed radiation necrosis with no active carcinoma. The patient's cytology remains clear and MRI abnormalities in the dura mater of the spine remain stable (axial view, top right; coronal view, bottom right).

Few treatment options exist for the treatment of carcinomatosis. A review of the current literature reveals an increase in case reports of patients who received treated with direct intrathecal administration of trastuzumab.[1-12] Patient survival has been reported to range from 39 days to more than 72 months, and the drug appears to be well tolerated with no clear adverse events attributed to it. Doses ranged from 5 to 100 mg. Intrathecal trastuzumab appears to be safe and effective in this patient population that has carcinomatosis meningitis caused by HER2-positive breast cancer.

The literature about the administration of trastuzumab and other mononclonal antibodies directly into the CSF of patients is developing.

References

1. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastasis in women who receive trastuzumab-based therapy for metastatic breast cancer. *Cancer*. 2003;97(12):2972-2977.

2. Platini C, Long J, Walter S. Meningeal carcinomatosis from breast cancer treated with intrathecal trastuzmab. *Lancet Oncol*. 2006; 7(9):778-780.

3. Stemmler HJ, Mengele K, Schmitt M, et al. Intrathecal trastuzmab (Herceptin) and methotrexate for meningeal carcinomatosis in HER2-overexpressing metastatic breast cancer: a case report. *Anticancer Drugs*. 2008;19(8):832-836.

4. Laufman LR, Forsthoefel KF. Use of intrathecal trastuzumab in a patient with carcinomatous meningitis. *Clin Breast Cancer*. 2001;2(3): 235.

5. Tsukada Y, Fouad A, Pickren JW, Lane WW. Central nervous system metastasis from breast carcinoma: autopsy study. *Cancer*. 1983; 52(12):2349-2354.

6. Glantz MJ, LaFollette S, Jaeckle KA, et al. Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. *J Clin Oncol*. 1999;17(10):3110-3116.

7. Mir O, Ropert S, Alexandre J, Lemare F, Goldwasser F. High-dose intrathecal trastuzumab for leptomeningeal metastases secondary to HER2 overexpressing breast cancer. *Ann Oncol*. 2008;19(11):1978-1980.

8. Pestalozzi BC, Brignoli S. Trastuzmab in CSF. *J Clin Oncol*. 2000;18(11):2349-2351.

9. Pegram M, Hsu S, Lewis G, et al. Inhibitory effects of combinations of HER2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers. *Oncogene*. 1999;18(13):2241-2251.

10. Oliveira M, Braga S, Passos-Coelho JL, Fonseca R, Oliveira J. Complete response in HER2+ leptomeningeal carcinomatosis from breast cancer with intrathecal trastuzumab. *Breast Cancer Res Treat*. 2011;127(3):841-844.

11. Plantini C, Long J, Walter S. Meningeal carcinomatosis from breast cancer treated with intrathecal trastuzumab. *Lancet Oncol*. 2006; 7(9);778-780.

12. Kosmas C, Malamos NA, Tsavaris NB, et al. Isolated leptomeningeal carcinomatosis (carcinomatous meningitis) after taxane-induced major remission in patients with advanced breast cancer. *Oncology*. 2002;63(1):6-15.