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CASE REPORT

Intrathecal trastuzumab for leptomeningeal carcinomatosis in patients with human epidermal growth factor receptor 2 positive breast cancer

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ABSTRACT

There has been recent increase in incidence of leptomeningeal carcinomatosis, possibly due to widespread use of adjuvant trastuzumab and its known poor CNS penetration. Currently there are limited therapeutic options for these patients and outcome is poor. We report two cases of women with HER2 positive breast cancer who developed leptomeningeal carcinomatosis for which they were treated with intrathecal trastuzumab in combination with systemic therapy. Both patients had rapid symptomatic benefit and radiological response and remained progression free for at least seven months. Intrathecal trastuzumab can be considered a reasonable therapeutic option for these difficult to treat patients.

Key words: *Her 2 positive breast cancer intrathecal trastuzumab, leptomeningeal carcinomatosis*

INTRODUCTION

Leptomeningeal carcinomatosis (LC) is a rare but fatal manifestation of metastatic breast cancer seen in approximately 3.5% of all breast cancer patients.[1,2] There has been recognition of the neurotropism property of human epidermal growth factor receptor 2 (HER2) positive subtype of breast cancer in recent years. An increasing incidence of leptomeningeal metastases has been reported in these patients, possibly due to widespread use of adjuvant trastuzumab that has increased systemic relapse-free survival without impacting the propensity for central nervous system (CNS) spread. This effect could, at least partly, be attributed to the poor CNS penetration of this antibody.[3,4] Currently, there are limited therapeutic options for these patients and the outcome is poor. We report two cases of women with HER2 positive breast cancer who were treated with intrathecal (IT) trastuzumab as part of their therapeutic regimen for LC.

CASE REPORTS

Case 1

In 2009, a 49-year-old premenopausal woman was diagnosed to have right breast cancer and synchronous bone metastases. She underwent modified radical mastectomy (MRM). Pathological evaluation revealed axillary nodal metastases and estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor (3+) were all positive by immunohistochemistry (IHC). She received six cycles of docetaxel, carboplatin, and trastuzumab, followed by maintenance adjuvant trastuzumab and tamoxifen. One year after completion of adjuvant trastuzumab, she developed liver metastases. She was started on capecitabine and lapatinib, on which she had a progression-free interval of 6 months. At this time, she was given six cycles of epirubicin and cyclophosphamide. At the end of this regimen, she presented with headache and vomiting. Magnetic resonance imaging (MRI) of the brain and spinal cord showed patchy leptomeningeal enhancement suggestive of LC. Her cerebrospinal fluid (CSF) examination revealed the presence of adenocarcinoma cells. She was treated with a combination of lapatinib, letrozole, and IT trastuzumab (50 mg 2 times/week for 4 weeks followed by 50 mg once per week for 4 weeks, followed by 150 mg once every 3 weeks) along with IT hydrocortisone (50 mg) on every occasion. She had rapid symptomatic improvement within 4 weeks of this treatment. The CSF cytology was negative for malignant cells after the 16 IT injections of trastuzumab. This treatment was well tolerated except for mild headache post-IT administration. She had symptomatic (increasing headache and vomiting) and radiological progression (new parenchymal brain lesion and diffuse increase in

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the leptomeningeal enhancement along both cerebral and cerebellar hemispheres) after 7 months of IT therapy. At this time, CSF cytology was also positive for malignant cells. On this occasion, she received whole-brain radiation therapy (WBRT) while IT trastuzumab was continued at 3 weekly intervals. The patient again had symptomatic improvement within 4 weeks and radiological response (decrease in parenchymal lesions and leptomeningeal enhancement) at 16 weeks.

Case 2

In 2011, a 62-year-old woman was diagnosed to have left locally advanced breast cancer (T3N1M0) which was ER and PR negative and HER2 positive (3+ by IHC). She was treated with neoadjuvant chemotherapy (12 cycles of weekly paclitaxel and trastuzumab) followed by MRM. This was followed by four more cycles of chemotherapy (epirubicin and cyclophosphamide) and locoregional radiation therapy. She received maintenance trastuzumab to complete a total of 1 year of this drug. Two months after completion of treatment, she presented with headache and vomiting. MRI of the brain revealed parenchymal metastases. She received WBRT followed by single agent lapatinib at the dose of 500 mg 2 times/day. After 4 weeks, she had good symptomatic improvement with resolution of headache and MRI revealed reduction in cerebral lesions. After 8 months of treatment with lapatinib, she developed headache, backache, and ataxia. A repeat MRI showed increasing brain metastases along with diffuse leptomeningeal enhancement. CSF cytology revealed adenocarcinoma cells consistent with LC. She was started on IT trastuzumab (150 mg every 3 weeks) combined every time with IT hydrocortisone (50 mg). She was simultaneously started on intravenous trastuzumab in usual doses, and lapatinib was escalated to 1250 mg/day. After the 2nd dose of IT trastuzumab, there was a significant clinical improvement, and the CSF cytology became negative for malignant cells. At the time of this report, she has completed 7 months of this treatment without evidence of disease progression and continues to be symptomatically well controlled.

DISCUSSION

The prognosis of breast cancer patients with leptomeningeal metastases remains dismal with a median survival of about 4.5 months.[5] Currently, there is no standard treatment because of its rarity and exclusion of patients from prospective trials. Little is known about the pharmacokinetics of trastuzumab in the CNS and its ability to cross the intact blood–brain barrier (BBB). Pestalozzi and Brignoli.[6] reported that CSF concentration of trastuzumab was 300 times lower than serum levels in a patient with LC, whereas Stemmler *et al*.[4] reported that trastuzumab may cross the impaired (due to radiation or carcinomatosis) BBB. In view of these facts, direct delivery of trastuzumab into the spinal fluid via IT administration seems to be a promising treatment option for HER2-positive breast cancer patients with LC.

Both our patients responded well to IT trastuzumab within 2–6 weeks of its initiation. They had rapid relief in their symptoms (headache, vomiting, dizziness, and ataxia) which led to marked improvement in their quality of life. Both patients showed clearance of carcinoma from CSF early in the course of treatment and objective response on CNS imaging. Further, both patients showed relatively prolonged periods of CNS disease control (7 and 7+ months, respectively). Of note, in parallel with evidence in systemic non-CNS metastatic disease, we continued IT trastuzumab beyond progression in the first patient. This strategy has been reported to be effective in 75% of cases in a recently published systematic review of patients with LC.[7]

There is no consensus on the optimal dosing and frequency of IT trastuzumab. The dose has varied from 5 to 150 mg and dosing interval from 2 times/week to once every 3 weeks.[7] We chose to use the higher dose (150 mg) at 3 weeks intervals in both patients because of long drug half-life,[8] anticipated safety and patient convenience. To the best of our knowledge, this dose and schedule of IT trastuzumab have been reported in only one patient till date.[9] In both of our patients, this dose and schedule proved to be well tolerated, and there was no evidence of anaphylaxis, aseptic meningitis, paraparesis, cauda equina fibrosis, or segmental root demyelination in our patients.

Although both patients showed good symptomatic, cytological, and radiological response, we cannot ascribe these results solely to IT trastuzumab because of concomitant use of systemic therapy that included HER2 targeted agents. However, the early temporal correlation of symptomatic and cytological response with initiation of IT treatment leads us to believe that the latter was at least partly responsible for the outcome.

CONCLUSION

IT trastuzumab, in the dose and schedule described in our report, led to significant symptomatic benefit without major toxicity in heavily pretreated HER2 positive breast cancer patients with LC. It should be considered as a reasonable therapeutic option in this clinical scenario.

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Conflicts of interest

There are no conflicts of interest.

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