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Progressive Central Nervous System Metastases in Responder Patients for Outside Central Nervous System Metastases on Trastuzumab-Based Therapy —Report of Two Cases of Refractory Breast Cancer

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ABSTRACT

We report two cases of central nervous system (CNS) metastases during systemic response to trastuzumab in combination with chemotherapy for refractory breast cancer. The patients responded to trastuzumab in combination with chemotherapy. During combination treatment, the patients developed cerebellar metastases. A follow-up computed tomography scan revealed that their diseases continued to respond outside the CNS. These cases suggest that the failure of trastuzumab to cross the blood-brain barrier may compromise its overall effectiveness and raises the possibility that CNS metastasis may become clinically more significant in patients receiving antibody-based therapies, including patients responding to therapy outside the CNS. Additionally, repeated stereotactic radiosurgery as gammaknife combination therapy synchronously with systematic trastuzumab-based therapy was useful for the treatment of metastatic breast carcinoma.

Key words: *Breast cancer, Trastuzumab, Stereotactic radiosurgery (SRS), Central nervous system (CNS) metastasis*

Approximately 25–30% of all human breast carcinomas over express human epidermal growth factor receptor-2/neu (HER-2/neu)[1], a member of the epidermal growth factor receptor family, and these patients may have a poor prognosis due to relative resistance to both hormonal therapy and chemotherapy[2,8]. However, the treatment of selected patients with trastuzumab, humanized anti-HER-2/neu antibodies in combination with chemotherapy, has been of benefit to patients with HER-2/neu over expressed metastatic breast cancer[3,10]. Recently, a case of CNS (central nervous system) progression in the face of continued peripheral response in a patient receiving trastuzumab in combination with chemotherapy was reported[11]. The peak concentrations of trastuzumab achieved in the CNS were lower than that of peripheral blood[11], suggesting a failure to achieve therapeutic concentrations in the CNS, limiting their effectiveness.

We encountered two similar cases. Metastatic breast carcinoma to the CNS may be more common among patients receiving trastuzumab-based therapy, including patients responding to therapy outside the CNS. New treatment strategies adding trastuzumab in combination with chemotherapy for metastases outside CNS and stereotactic radiosurgery (SRS) for CNS may extend the survival of selected patients.

CASE REPORT

Case 1: a 36-year-old woman was diagnosed with stage IIA (UICC-TNM) cancer, and underwent modified radical mastectomy in September 1997. She had refractory breast cancer based on disease progression in January 2000 despite neoadjuvant therapy with CAF + TAM and treatment of the metastatic disease with docetaxel + cisplatin as the first-line therapy. Immunohistochemical analysis (Herceptest™) showed the HER2 status of the tumor to be 2+. Disease progression on docetaxel + cisplatin, trastuzumab/paclitaxel

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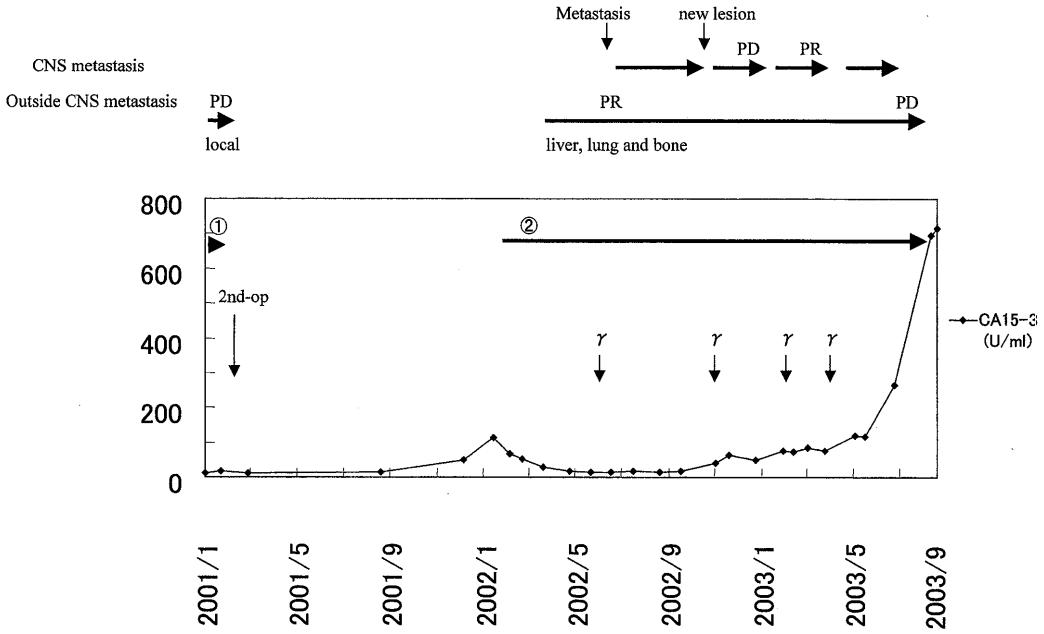


2nd-op: simple mastectomy for local recurrence after breast conserving therapy. ①: docetaxel, ②: paclitaxel weekly + H
γ: gamma knife therapy, CNS: Central Nervous System, H: trastuzumab

Fig. 1. Clinical course of case 1.

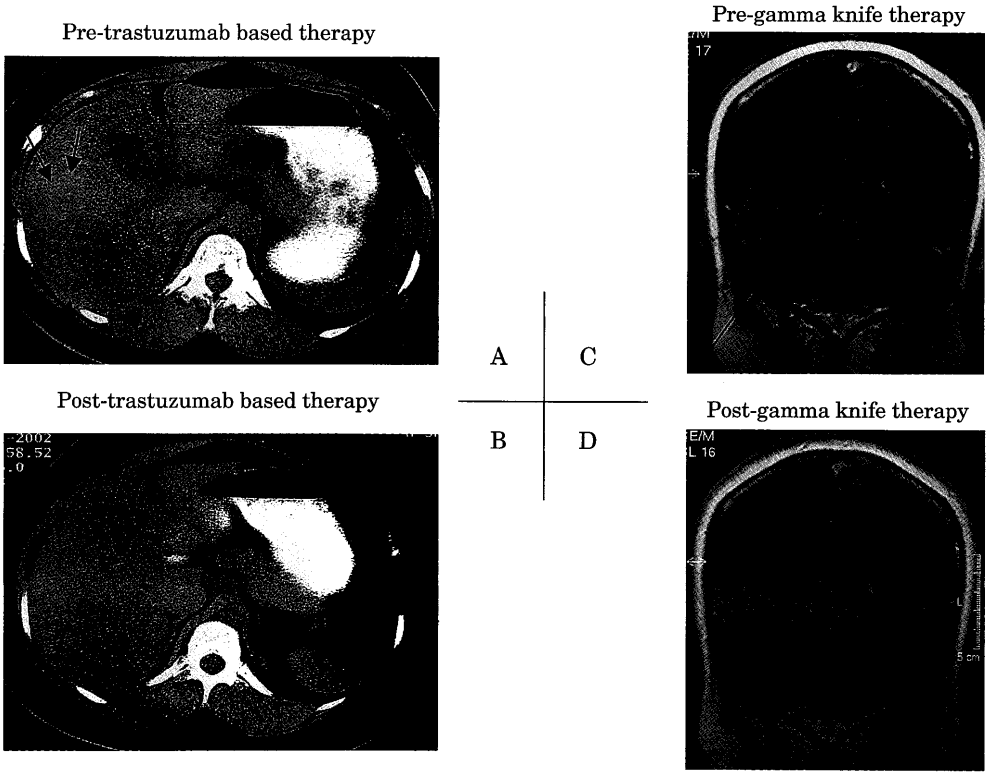
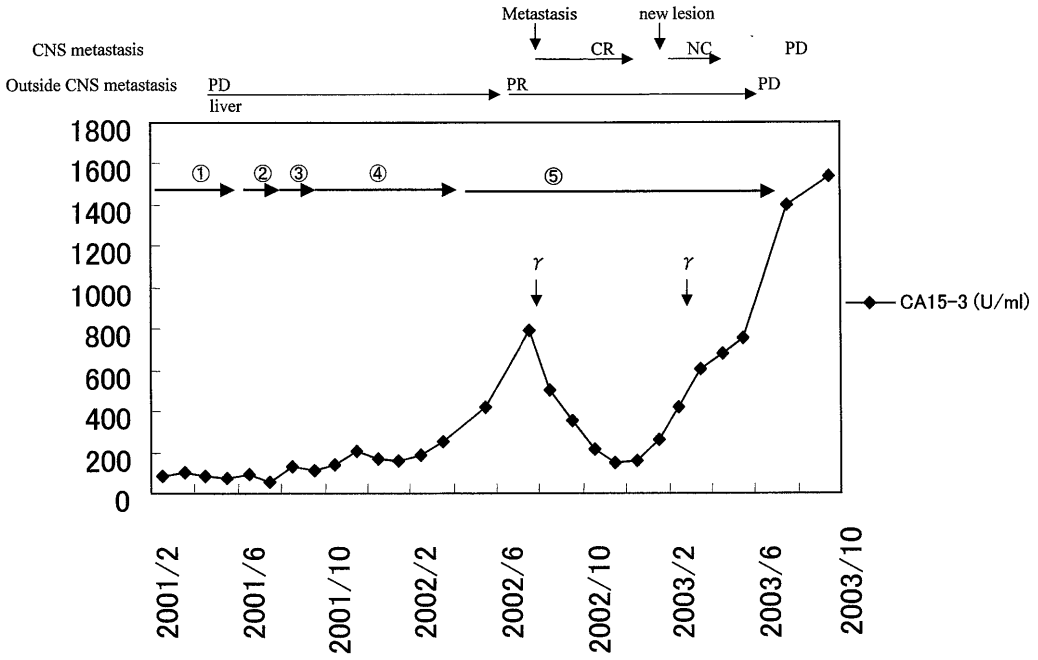


Fig. 2A. March 2002: computed tomography of the abdomen prior to trastuzumab-based therapy revealed multiple liver metastases in case 2.
Fig. 2B. December 2002: computed tomography of the abdomen after 2 courses of trastuzumab-based therapy in case 2.
Fig. 2C. June 2002: computed tomography of the head revealed brain metastasis in case 2.
Fig. 2D. February 2003: computed tomography of the head after gamma knife therapy in case 2.



①: CAF(cyclophosphamide+doxorubicin+5-fluorouracil), ②: paclitaxel weekly, ③: doxifluridine+medroxyprogesterone acetate, ④: paclitaxel weekly+H, ⑤: vinorelbine+H.
γ: gamma knife therapy, CNS: Central Nervous System, H: trastuzumab

Fig. 3. Clinical course of case 2.

was initiated and a partial response (PR) was observed in the liver, lungs and bone. Improvement of the systemic disease was maintained over 14 months. While on trastuzumab/paclitaxel, she developed CNS metastases while continuing to respond in the liver, lung (complete response (CR)), and bone (PR). While gamma knife therapy was performed in June 2002, November 2002, February 2003 and April 2003, the patient continued to receive systemic therapy for 17 months and with continued disease stability through November 2003 (Fig. 1).

Case 2: a 32-year-old woman was diagnosed with stage IV (UICC-TNM) breast cancer in February 2001. Herceptest™ showed the HER2 status of the tumor to be 2+. As the disease progressed in the liver (Fig. 2A), lungs and chest wall with CAF as the first-line therapy, docetaxel as the second line, 5'-DFUR+MPA as the third line and trastuzumab/paclitaxel as the fourth line, trastuzumab/vinorelbine was initiated and PR was observed in the liver (Fig. 2B), lungs and chest wall. Improvement of the systemic disease was maintained over 7 months. Although response continued in the liver, lung and mediasternum lymph node (PR) with trastuzumab/vinorelbine therapy, she developed CNS metastases (Fig. 2C). While gamma knife therapy was performed in June 2002 and February 2003, the patient continued to receive systemic treatment for 17 months after the diagnosis of CNS disease and with continued stability of disease through November 2003 (Fig. 2D, Fig. 3).

DISCUSSION

In our cases, CNS disease progressed in the face of continued peripheral response in a patient receiving trastuzumab in combination with chemotherapy. After CNS metastases were diagnosed, follow-up computed tomography scan revealed that their disease continued to respond outside the CNS. This suggested a failure to achieve therapeutic concentrations of the agents in the CNS. Although little is known about the penetration of trastuzumab across the blood-brain barrier, it is likely that it penetrates poorly based on its size and charge. CNS levels of trastuzumab were measured in a patient receiving treatment for carcinomatous meningitis. Peak concentrations achieved in the CNS were 300-fold lower than in the peripheral blood, at 210 ng/ml and 61,392 ng/ml, respectively[9]. This report suggested a failure to achieve therapeutic concentrations of the agents in the CNS, thereby limiting their effectiveness. On the other hand, HER-2/neu-positive breast carcinoma is a more aggressive subtype of the disease, possibly leading to a high risk of CNS metastases[6]. Trastuzumab-based therapy sufficiently extends survival in some patients to reach metastasis to the CNS.

Today, most chemotherapeutic agents have lower activity on CNS metastases compared to other sites of metastatic disease because of poor penetration of the blood-brain barrier[4,7]. Recently SRS has been used to treat metastatic brain tumors. For patients with 2 to 4 brain metastases, a randomized study indicated that combined

whole-brain radiation therapy (WBRT) and SRS improve local control, but not survival significantly more than WBRT alone[5]. In our cases, repeated stereotactic radiosurgery as gamma knife combination therapy synchronously with systematic trastuzumab-based therapy was useful for the treatment of metastatic breast carcinoma.

New treatment strategies adding trastuzumab in combination with chemotherapy for metastases outside CNS, and SRS for CNS metastases, including salvage therapy after intracranial failure, may extend survival after the diagnosis of CNS metastases for selected patients.

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