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Complete Response of Severe Symptomatic Bone Marrow Metastases from Heavily Pretreated Breast Cancer with a 3-Weekly Trastuzumab Schedule. A Clinical Case

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Abstract. *Overexpression of HER-2/neu in breast cancer has been associated with more aggressive disease and poor overall survival. Trastuzumab, a recombinant humanized monoclonal antibody with high affinity for the HER-2 protein, inhibits the growth of breast cancer cells overexpressing HER-2. Trastuzumab showed, as second-line treatment, 15% of objective response in metastatic breast cancer. Bone marrow metastases are detectable in 23% of the patients with advanced breast cancer at first relapse and this rate increases in patients with metastatic disease. We report a case of a complete response of bone marrow metastases from breast cancer using a 3-weekly trastuzumab schedule, in a heavily pretreated patient with severe symptomatic pancitopenia.*

HER-2/neu, a member of the group I growth factor receptor family, is a tyrosine-kinase membrane receptor which, when activated, induces a phosphorylation cascade in cytoplasmic kinases leading to increased transcription of nuclear proteins and cellular growth. It is amplified and/or overexpressed in 20% to 30% of patients with breast cancer (1). Overexpression of this oncogene product is associated with increased rates of tumour growth, enhanced rates of metastasis, shorter disease-free survival and overall survival (1-4). Patients with HER-2/neu-overexpressing tumours have more aggressive and more malignant courses. HER-2/neu has been targeted by monoclonal antibodies, immunoconjugates, vaccines, antibody-directed enzyme prodrug therapy, antisense therapy and gene therapy (5).

Trastuzumab is a humanized monoclonal antibody against the extracellular domain of HER-2/neu (6). Trastuzumab resulted in 15% objective response in metastatic breast cancer (MBC) as second-line treatment (7). The combination of chemotherapy plus trastuzumab in first-line treatment resulted in 50% objective response *versus* 32% of chemotherapy alone in MBC patients (8). Trastuzumab is well tolerated and low grade fever, chills, fatigue and constitutional symptoms occur primarily with the first infusion and serious adverse effects are not frequent (5).

In 23% of the patients with advanced breast cancer, bone marrow metastases are detectable at first relapse and this rate even increases in patients with metastatic disease. However, a significant percentage of women with primary breast cancer have a micrometastatic disease in the bone marrow which is regularly underestimated by current clinical and pathological staging procedures (9).

Case Report

In December 1999, a 51-year-old woman received a left quadrantectomy due to a poorly-differentiated (G 3) invasive ductal carcinoma of the breast. The stage of the disease was T1N0M0 (stage I). Prognostic factors were: oestrogen receptors (ER) and progesterone receptors (PR)-negative, Ki-67=20% and c-erb-B2 score 3 + with the immunohistochemical (IHC) methods. Six cycles of CMF regimen (cyclophosphamide plus methotrexate plus 5-fluorouracil) were administered in an adjuvant setting followed by radiotherapy. No additional adjuvant treatment was administered. The follow-up was negative up to June 2001 when the patient developed multiple bilateral lung metastases. She received six cycles of epirubicin plus paclitaxel and letrozole, reaching a complete response lasting

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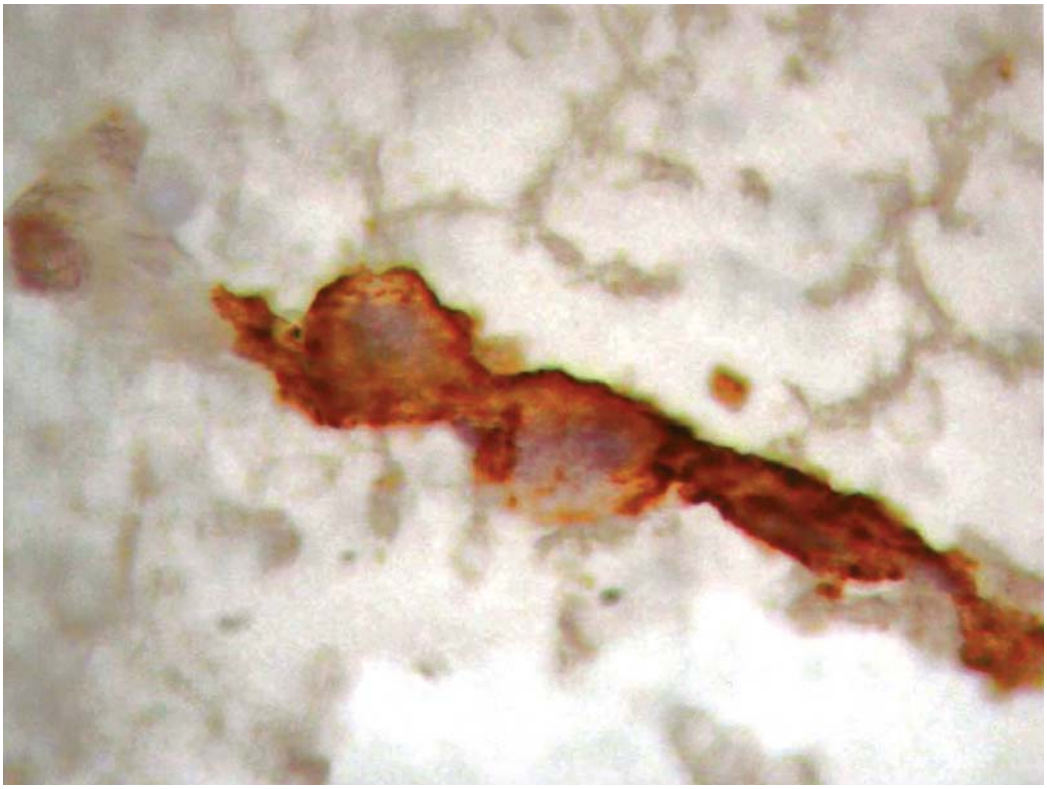

Figure 1. *Malignant epithelial cells showing a strong and continuous membrane immunostaining.*

3 months. In December 2001, due to lung progression, 3 cycles of irinotecan plus docetaxel chemotherapy were administered up to February 2002, inducing a stable disease. In May 2002, a bone scan revealed bone metastases at cervical (C3, C7), thoracic (T10) and lumbar (L4) vertebrae and sacroiliac articulation confirmed by MRI. Palliative radiotherapy was administered for bone metastases, letrozole was stopped and treatment with zoledronic acid started.

The patient was referred to our Institution in October 2002 with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 3, leukopenia (1200/mm^2), anemia, (haemoglobin 7.5 g/dL), and severe symptomatic (multiple petechias and hematomas) thrombocytopenia (platelets 5000/mm^2). Red blood packets and platelet transfusions were performed. A bone marrow aspiration showed metastatic involvement. In fact, bone marrow smears revealed scattered clusters of malignant epithelial cells. Stored air-dried smears were utilised for IHC study. The smears were post-fixed in acetone for 20 minutes and rinsed in buffer. The IHC determination was performed by DAKO Hercep-test kit, following the manufacturer's recommendations. A strong and continuous membrane staining was observed in most malignant cells (3+ positivity) (Figure 1). After cardiac function evaluation with ECG and echocardiography, treatment with trastuzumab 8 mg/kg intravenous (*i.v.*) as loading dose and then 6 mg/kg *i.v.* every 3 weeks was started. After the first administration of trastuzumab, the patient achieved a complete recovery of blood cells count and symptoms with a PS improvement (PS 1). After 6 trastuzumab administrations, CT scans and bone MRI showed a stable disease. After 8 trastuzumab administrations the patient progressed due to a pleural effusion despite the persistence of complete blood cells count recovery. Trastuzumab was stopped and capecitabine chemotherapy was administered for 3 cycles with a progression of lung metastases and a worsening of PS (PS 3). The patient died in July 2003 due to a further progression of disease. She sustained complete blood cells count recovery from the beginning of the trastuzumab administration up to her death.

Discussion

The medical approach to the management of MBC has changed through the years following the introduction in clinical practice of new cytotoxic drugs and biologic agents. Combination chemotherapy is usually the initial treatment of

choice for ER- and PR-negative MBC patients. The average survival time after the diagnosis of MBC is 18 to 24 months, but this varies widely according to the metastatic sites of the disease. The median survival time has traditionally been lower for patients with visceral disease (6 to 13 months) *versus* those with only bone disease (18 to 30 months) (10).

A humanized version of a murine antibody directed against the extracellular domain of HER-2 has been developed for the treatment of patients with breast cancer whose tumours overexpress HER-2. Many trials have used trastuzumab, either alone or in combination with chemotherapy, highlighting the potential impact of this novel anticancer treatment in the management of patients with MBC who overexpress HER-2 (10). In these trials a weekly schedule, based on the clearance of the antibody in preclinical studies, was used. In most cases, a loading dose of 4 mg/kg *i.v.* was used followed by 2 mg/kg *i.v.* weekly until disease progression (11).

For this patient, considering poor PS and the possible difficulties of a weekly outpatient-basis schedule, a 3-weekly schedule was used. A recent trial evaluated trastuzumab 8 mg/kg as loading dose followed by 6 mg/kg every 3 weeks in HER2-positive MBC, showing this schedule to be convenient, well tolerated and efficacious, and having the same dose-intensity (2 mg/kg/week) as weekly administration (12). Several clinical trials using this innovative schedule are ongoing. Moreover, three phase I trials reported the serum half-life of trastuzumab to be augmented with the increasing of the dose; in fact it ranged from approximately 1 day in the low-dose group (10 mg) to 2 weeks in the highest dose group (500 mg) (11).

To the best of our knowledge, this is the first case in which a clinical complete response of bone marrow metastases from heavily pretreated breast cancer was reported using trastuzumab. In our opinion it is of particular interest that the response was reported in a heavily pretreated patient with poor PS and severe symptomatic pancitopenia, for which further and more aggressive treatments, such as chemotherapy, were excluded and trastuzumab seemed to be the only therapeutic option.

References

1 Press MF, Jones LA, Godolphin W *et al*: HER-2/neu oncogene amplification and expression in breast and ovarian cancers. Prog Clin Biol Res *354A*: 209-221, 1990.

2 Slamon DJ, Godolphin W, Jones LA *et al*: Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science *244*: 707-712, 1989.

3 Liu Y, El-Ashry D, Chen D *et al*: MCF-7 breast cancer cells overexpressing transfected c-erbB-2 have an *in vitro* growth advantage in estrogen-depleted conditions and reduced estrogen-dependence and tamoxifen-sensitivity *in vivo*. Breast Cancer Res Treat *34*: 97-117, 1995.

4 Ragaz J, Brodie A, Jelovac D *et al*: Expression of COX2, aromatase, HER-2/neu and their correlation with the long-term outcome of 930 stage I-III breast cancer (BrCa) patients. Results from the British Columbia (BC) Tissue Micro-Array Project (BCTMAP). Proc Am Soc Clin Oncol *22*: 3 (abstr. 9), 2003.

5 Hortobagyi GN: Options for treatment of metastatic breast cancer. *In*: ASCO Educational Book, 1990, pp. 515-521.

6 Hudziak RM, Lewis GD, Winget M *et al*: p185HER2 monoclonal antibody has antiproliferative effects *in vitro* and sensitizes human breast tumor cells to tumor necrosis factor. Mol Cell Biol *9*: 1165-1172, 1989.

7 Cobleigh MA, Vogel CL, Tripathy D *et al*: Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol *17*: 2639-2648, 1999.

8 Slamon DJ, Leyland-Jones B, Shak S *et al*: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpress HER2. New Engl J Med *344*: 783-792, 2001.

9 Kasimir-Bauer S, Oberhoff C, Schindler AE and Seeber S: A summary of two clinical studies on tumor cell dissemination in primary and metastatic breast cancer: methods, prognostic significance and implication for alternative treatment protocols. Int J Oncol *20*: 1027-1034, 2002.

10 Perez EA: Current management of metastatic breast cancer. Sem Oncol *26 (Suppl. 12)*: 1-10, 1999.

11 Shak S: Overview of the trastuzumab (herceptin) anti-HER2 monoclonal antibody clinical program in HER2-overexpressing metastatic breast cancer. Sem Oncol *26 (Suppl. 12)*:71-77, 1999.

12 Carbonell Castellon X, Castaneda-Soto NJ, Clemens M *et al*: Efficacy and safety of 3-weekly herceptin (H) monotherapy in women with HER2-positive metastatic breast cancer (MBC): preliminary data from a phase II study. Proc Am Soc Clin Oncol *21*: 19a (abstr. 73), 2002.

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