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CASE REPORT

HER-2 overexpression and targeted treatment by trastuzumab in a very old patient with gastric cancer

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Abstract. Inui T, Asakawa A, Morita Y, Mizuno S, Natori T, Kawaguchi A, Murakami M, Hishikawa Y, Inui A (Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima; and Kinki University School of Medicine, Osaka, Japan). HER-2 overexpression and targeted treatment by trastuzumab in a very old patient with gastric cancer (Case report). *J Intern Med* 2006; **260:** 484–487.

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An 88-year-old, previously healthy man presented with mild appetite loss in November 2001. Physical examination was normal and laboratory tests revealed mild anaemia and renal dysfunction but no abnormal liver function. A slight increase was observed in tumour markers such as carcinoembryonic antigen (CEA) (7.7, normal < 2.5 ng mL^{-1}) and CA19-9 (370, normal < 37 U mL^{-1}). Ultrasound sonography showed a liver mass (15.9 × 15.9 mm, S5). Positron-emission tomography with [18F] fluorodeoxyglucose as a tracer indicated multiple liver metastases and increased accumulation of [18F] fluorodeoxyglucose in the stomach (Fig. 1a). Esophagogastroduodenoscopy disclosed Borrmann III type advanced gastric cancer (Fig. 2a). Microscopic examination of gastric biopsy specimens revealed adenocarcinoma with papillotubular cell types. Liver metastasis (Fig. 2c) but no pulmonary, bone or brain metastasis was observed by computed tomography, magnetic resonance imaging or bone scintigram. The clinical stage of this patient was according to the TNM classification of malignant tumours. The patient was treated mildly from February 2002 with capecitabine in the outpatient clinic, but the liver metastasis progressed in size, reaching the maximum of 56.4 × 48.2 mm by May 2002.

Assessment of HER-2 (ErbB-2) gene amplification and protein expression was performed by fluorescence *in situ* hybridization and immunohistochemistry in our laboratory. It revealed markedly increased HER-2 gene amplification (red colour in Fig. 1b, signal ratio 5.3, normal <2.0) and protein expression (+3) (Fig. 1c), as well as increased protein expression of epidermal growth factor receptor (EGFR, Fig. 1d)) and platelet-derived growth factor receptor α (PDGFRα, Fig. 1e) but not of c-kit (Fig. 1f). The patient and family then chose to participate in the study of trastuzumab combined with proton ion beam therapy. Trastuzumab (3 mg kg^{-1}) was delivered intravenously every week in the outpatient clinic in June 2002. The patient received prophylactic hydrocortisone and granisetron for potential infusion reaction. One month after the start of trastuzumab treatment, the size of the hepatic metastasis was markedly reduced (21.3 × 21.3 mm by ultrasound sonography). It reached the nadir of 13.1 × 13.9 mm in February 2003. That level was maintained thereafter with low doses of 5-fluorouracil derivative (Fig. 2d), which was replaced for capecitabine because of intractable hand-foot syndrome. The primary tumour at the stomach also responded well to the treatment (Fig. 2b); the patient remained clinically

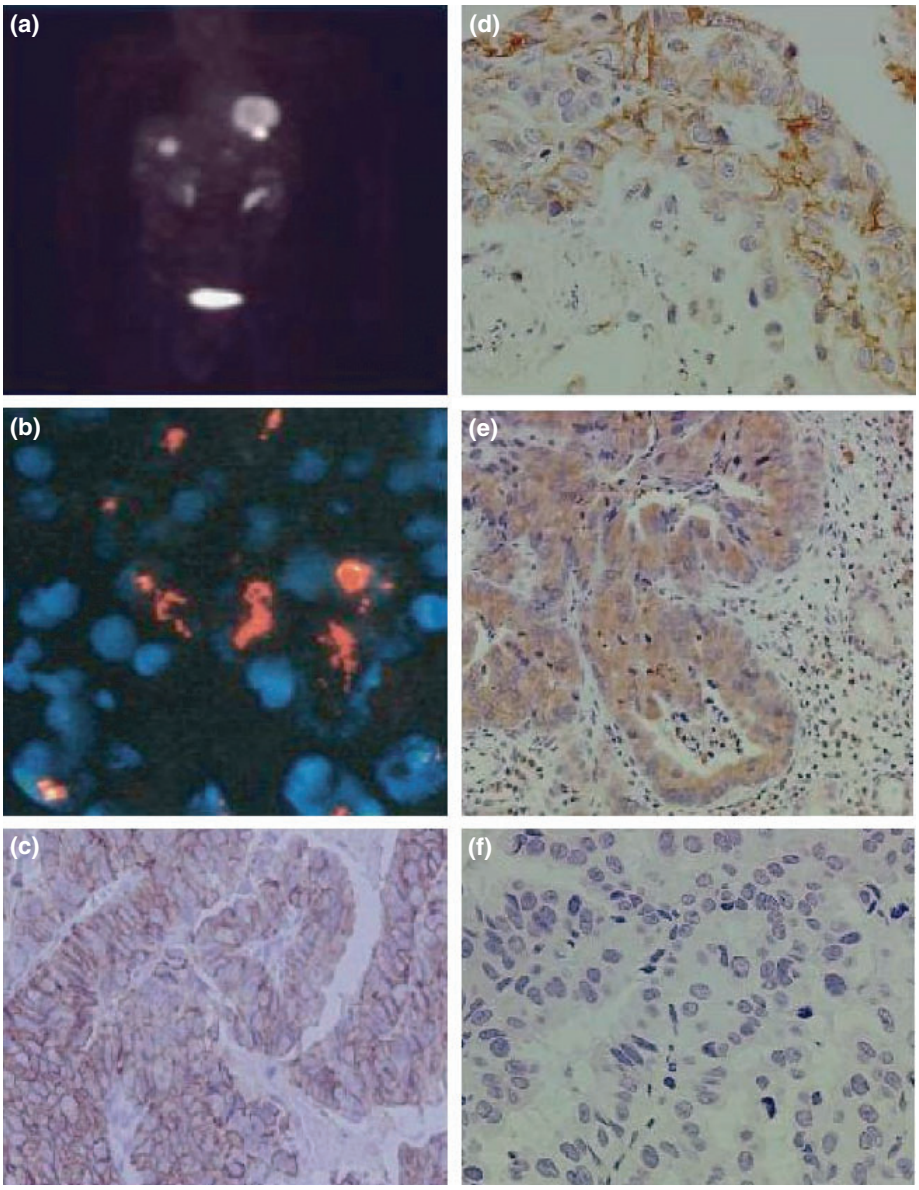

Fig. 1 (a) Positron-emission tomography studies with [^{18}F] fluorodeoxyglucose as the tracer. Abnormal uptake of [^{18}F] fluorodeoxyglucose was seen in the liver and the stomach, as well as in the lymph node around the head of the pancreas, (b), (c). Gastric adenocarcinoma showing overexpression of HER-2 protein (b amplification ×10) detected by immunohistochemistry and amplification of the HER-2 gene (c, amplification ×1000) detected by fluorescence in situ hybridization. Red color indicates HER-2 signal, whereas green is control, Increased proton expression of HER-1 (d) and PDGER alpha(e) but not of C-kit (f) are also shown.

well. The residual hepatic metastasis was destroyed by 150 MeV proton beam therapy for 8 days (totally 56 GyE) in July 2003 (Fig. 2e). The patient kept good performance status in March 2005 and showed no apparent cardiac dysfunction despite continued trastuzumab administration as evaluated by echocardiography. Modest dermatitis localized in the radiation area and slight increase in γ-GTP (23–78 U L^{-1}) were associated with proton ion beam therapy. Although the performance status remained relatively stable, the patient developed influenza pneumonia and died on 31 December 2005.

Proto-oncogenes, including the HER-2 (ErbB-2), represent a family of normal cellular genes involved in cell growth and differentiation [1–7]. There is much evidence that alterations in the structure of

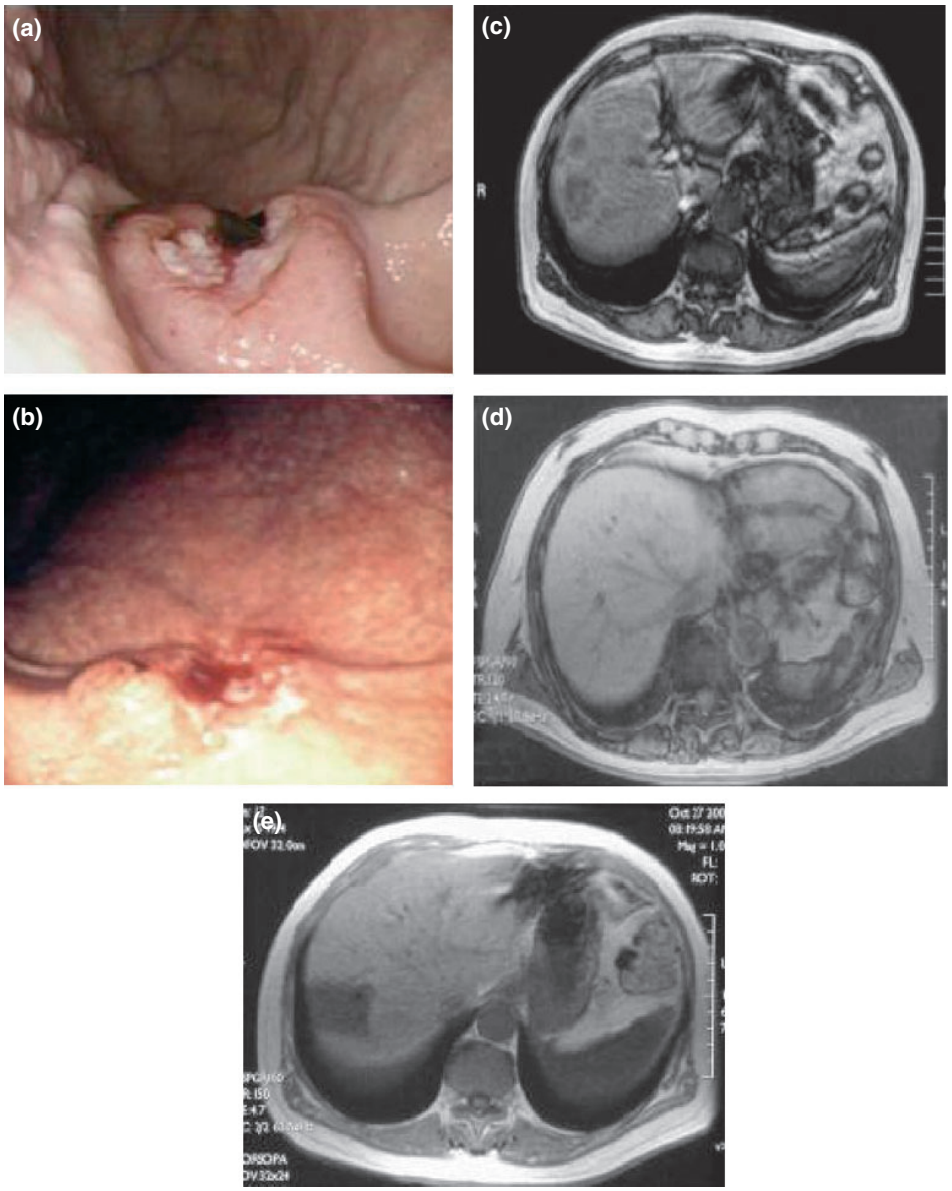

Fig. 2 (a), (b) Esophagogastroduodenoscopy. (c), (d) Transaxial T1-weighted MRI studies of the upper abdomen. A giant ulcerating carcinoma in the upper body of the stomach (a) and liver metastasis (c) were present before trastuzumab therapy. Gastric (b) and liver (d) tumors were markedly smaller after 10 mo treatment. The residual hepatic metastasis was completely destroyed by proton ion beam (e).

these genes or their amplification or overexpression may play a role in the pathogenesis of breast, colon and other cancers. The HER-2 gene encodes a 185-kDa transmembrane protein with tyrosine kinase activity that shares approximately 50% of overall homology with EGFR (HER-1). Trastuzumab (Herceptin®, Chugai Pharmaceutical Co. Ltd, Japan) is a humanized monoclonal antibody directed against the HER-2. It is the first oncogene-targeted treatment for women with HER-2-positive breast cancer [7]. Strategies designed to employ HER-2 protein overexpression or gene amplification in therapy selection are warranted because they are associated with approximately one-fourth of all gastrointestinal tract malignancies [1–3]. We found dramatic and continued anti-tumour effects in a very old patient with HER-2-overexpressing gastric cancer with rapidly progressive liver metastasis. Gastric cancer remains the most frequent cause of cancer-related deaths worldwide [8]; in Japan,

gastric cancer typically causes several times as many deaths as breast cancer and is generally resistant to various chemotherapeutic agents.

To our knowledge, this is the first report in a very old patient which shows promise for treating HER-2-overexpressing advanced gastric cancer by trastuzumab [9], in successful combination with proton beam therapy that offers many advantages over conventional radiotherapy because of the different physical and radiological characteristics [10, 11]. Major response with stable disease sustained for more than 3 years with a good quality of life would be tantamount to a cure for such aged patients. Weekly trastuzumab treatment will be a useful foundation for combination treatment with other biological agents in HER-2-overexpressing cancer from the gastrointestinal tract, as shown in metastatic breast cancer for prolonged survival [7]. Gastric cancer cells of this patient also showed overexpression of EGFR and PDGFRα protein, which are cell surface, tyrosine kinase receptors involved in various cellular functions and tumour growth. More studies to examine the therapeutic potential are needed as blockers of EGFR (Gefitinib) and PDGFR (Imatinib Mesylate) signaling are already available in the clinical setting [2, 12–14]. Targeted chemotherapy offers the possibility of inhibiting specific dysregulated pathways in cancer cells of individual patient whilst having minimal effects on normal cell function. This is particularly important in the geriatric setting as old patients often cannot receive aggressive antineoplastic regimens that may produce intractable side effects and/or reduce the quality of life of such patients. Molecular definition of gastric cancer may thus represent a novel approach not only for the prognostic indicator [1, 4] but also for the personalized cancer therapy in future.

Conflict of interest statement

No conflict of interest was declared.

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References

1 Ross JS, McKenna BJ. The HER-2/neu oncogene in tumors of the gastrointestinal tract. *Cancer Invest* 2001; **19:** 554–68.
2 Barnard J. Epidermal growth factor receptor blockade: an emerging therapeutic modality in gastroenterology. *Gastroenterology* 2001; **120:** 1872–4.
3 Mann M, Sheng H, Shao J *et al.* Targeting cyclooxygenase 2 and HER-2/neu pathways inhibits colorectal carcinoma growth. *Gastroenterology* 2001; **120:** 1713–9.
4 Yonemura Y, Ninomiya I, Yamaguchi A *et al.* Evaluation of immunoreactivity for erbB-2 protein as a marker of poor short term prognosis in gastric cancer. *Cancer Res* 1991; **51:** 1034–38.
5 Inui A. Targeted therapy in cancer and transgenic animal model. *Cancer Invest* 2003; **21:** 819–20.
6 Kapitanovic S, Radosevic S, Kapitanovic M *et al.* The expression of p185 (HER-2/neu) correlates with the stage of disease and survival in colorectal cancer. *Gastroenterology* 1997; **112:** 1103–13.
7 Slamon DJ, Leyland-Jones B, Shak S *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344:** 783–92.
8 van de Velde CJ, Peeters KC. The gastric cancer treatment controversy. *J Clin Oncol* 2003; **21:** 2234–6.
9 Rebischung C, Barnoud R, Stefani L *et al.* The effectiveness of trastuzumab (Herceptin) combined with chemotherapy for gastric carcinoma with overexpression of the c-erbB-2 protein. *Gastric Cancer* 2005; **8:** 249–52.
10 Kagawa K, Murakami M, Hishikawa Y *et al.* Preclinical biological assessment of proton and carbon ion beams at Hyogo Ion Beam Medical Center. *Int J Radiat Oncol Biol Phys* 2002; **54:** 928–38.
11 Weyrather WK, Debus J. Particle beams for cancer therapy. *Clin Oncol (R Coll Radiol)* 2003; **15:** S23–8.
12 Paez JG, Janne PA, Lee JC *et al.* EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. *Science* 2004; **304:** 1497–500.
13 Joensuu H, Roberts PJ, Sarlomo-Rikala M *et al.* Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001; **344:** 1052–6.
14 Kaklamani V, O'regan RM. New targeted therapies in breast cancer. *Semin Oncol* 2004; **31:** 20–5.

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