Long-term remission of excessive liver metastases in a breast cancer patient with chronic alcohol abuse using a monotherapy with trastuzumab

Michael H. R. Eichbaum[a], Andreas Schneeweiss[a] and Gunther Bastert[a]

We report on the successful treatment of a 43-year-old breast cancer patient with excessive liver metastases and chronic alcohol abuse. After first occurrence of hepatic metastases, systemic and interventional therapies were performed, and resulted in short-term partial remission. Finally, an excessive progression of the hepatic metastases was diagnosed. A systemic therapy with weekly trastuzumab (Herceptin) infusions was induced and a complete remission was achieved that is ongoing now for over 45 months. ***Anti-Cancer Drugs*** **16:199–200 © 2005 Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2005, **16:**199–200

Keywords: alcohol abuse, breast cancer, liver metastases, trastuzumab

[a]Department of Gynecology and Obstetrics, University of Heidelberg Medical School, Heidelberg, Germany.

Correspondence to M. H. R. Eichbaum, University of Heidelberg Medical School, Department of Gynecology and Obstetrics, Voss-Strasse 9, 69115 Heidelberg, Germany.
Tel: +49 6221 56 37345; fax +49 6221 56 8599;
e-mail: Michael_Eichbaum@med.uni-heidelberg.de

Received 26 July 2004 **Revised form accepted** 14 October 2004

Introduction

The prognosis of patients with disseminated liver metastases from breast cancer is poor. A median survival of 1–14 months after first diagnosis of hepatic metastases is reported [1]. Breast cancer liver metastases are considered to be less responsive to chemotherapy and, furthermore, a relevant hepatic dysfunction often limits the possibility of delivering standard dose regimen [2,3].

The humanized monoclonal antibody trastuzumab (Herceptin; Genentech, South San Francisco, CA) is a safe and well-tolerated agent approved for the therapy of HER2-overexpressing metastatic breast cancer [4–6]. Herceptin single-agent therapies are reported to have response rates up to 35% in HER2-overexpressing metastatic breast cancer [6]. The presented case shows an excellent, long-term remission of excessive breast cancer liver metastases using monotherapy with trastuzumab after cytotoxic and interventional pre-treatment. Remarkably, the reported patient suffers from chronic alcohol abuse that is ongoing for years.

Case report

We report on a 43-year-old patient with liver metastases from breast cancer who presented at our clinic for further therapy. Primary therapy consisted of mastectomy with histological proof of a low-graded pT2 pN1b invasive ductal carcinoma. Estrogen and progesterone receptors were negative and an overexpression of the HER2 protein was found (3 + by immunohistochemistry with Herceptest). Adjuvant chemotherapy was performed with 4 cycles of epirubicin/cyclophosphamide (90/600 mg/m^2 day 1 q 3 weeks), followed by 3 cycles of a CMF regimen (500/40/600 mg/m^2 day 1, 8 q 4 weeks).

Eight months after primary therapy the first occurrence of hepatic metastases was diagnosed. Six cycles of a chemotherapy with gemcitabine resulted in a partial remission with a single residual lesion of about 2 cm (ultrasound). Subsequently, two interventions of laser-induced thermoablation therapy were performed, but only 2 months later was a massive progression with disseminated liver metastases detected by computed tomography (CT) scan. Liver enzymes were significantly elevated: CEA was at 2.6 µg/l, Ca 15-3 at 41 U/ml.

In addition to the metastatic breast cancer, this patient was suffering from chronic alcohol abuse for several years with a maximum of more than two bottles of wine per day.

We started systemic therapy with infusions of trastuzumab in weekly applications of 2 mg/kg body weight after a loading dose of 4 mg/kg body weight. Echocardiography was normal at the beginning of the therapy and no significant change occurred. Liver enzymes and tumor marker levels normalized rapidly, and 4 months later a complete remission of all hepatic lesions was found by CT scan. The patient is actually in fine condition and the alcohol consumption has decreased, but is still chronic. The remission of the liver metastases is now ongoing for over 45 months.

Discussion

There is increasing evidence that trastuzumab is an effective drug in treatment regimens for HER2-overexpressing metastatic breast cancer, not only in combination with cytotoxic agents, but also as single-agent therapy in settings of chemotherapy resistance [4–7]. Several authors report successful remissions of metastatic

0959-4973

breast cancer using trastuzumab single-agent therapies. Takahashi *et al.* achieved a good clinical remission of bone and lymph node metastases after chemo-endocrine pre-treatment with severe myelotoxicity [8]. Rossi *et al.* found a complete remission of symptomatic bone marrow metastases after heavy cytotoxic pre-treatment [9]. Finally, Sawaki *et al.* present 27 pre-treated patients, but found durable response rates only in cases with non-visceral metastases [10].

The chronic alcohol abuse in this patient with initially disseminated hepatic lesions merits special attention. The possible molecular interactions between ethanol and breast cancer cells have not yet been clearly elucidated. Singletary *et al.* showed that ethanol, added in physiologically relevant concentrations, enhances cell proliferation in ER-positive breast cancer cell lines, whereas ER-negative cell lines were not influenced [11]. Fan *et al.* found a dose-dependent increase up to 10- to 15-fold in the transcriptional activity of the liganded estrogen receptor (ERα) after ethanol exposure to MCF-7 and T47D cell lines [12].

Different effects of ethanol on the growth of human breast cancer cells were described by Izevbigie *et al. in vitro* [13]. In their experiments, stimulation of MCF-7 cells with ethanol at physiologically relevant concentrations (0.3%) resulted in a significant increase of cell growth of more than 200%. These results completed the findings from Meng *et al.* who had already reported a significant stimulation of cell adhesion, migration and invasion of MCF-7 cells by physiological concentrations of ethanol [14].

Another possible interaction between ethanol and breast cancer cells was shown by Zhu *et al.* [15]. In an *in vitro* study, the authors found an ethanol-induced alteration of the expression of the ribosomal large subunit protein rpL7a in T47D cells, which could mediate transformation, tumor growth and aggressiveness in breast cancer.

Luo *et al.* studied the effects of ethanol on the migration of breast cancer cells in culture, with special regard to the erbB growth factor receptors [16]. An increased expression of erbB2, erbB3 and erbB4 after ethanol exposure was found with a modest increase of the invasion potential of the T47D cells studied. Interestingly, knocking out erbB2 with anti-sense oligonucleotides could block the ethanol-induced migration of the breast cancer cells. Possibly, this phenomenon could in part explain the efficacy of the trastuzumab therapy in the presented patient.

The reported case underpins the therapeutic option of Herceptin single-agent therapy even in settings of massive pre-treatment and resistance to chemotherapy. Whether the chronic consumption of alcohol influenced the successful remission of the hepatic lesions remains speculative.

References

1 Wyld L, Gutteridge E, Pinder SE, James JJ, Chan SY, Robertson JFR, *et al.* Prognostic factors for patients with hepatic metastases from breast cancer. *Br J Cancer* 2003; **89**:284–290.

2 Zinser JW, Hortobagyi GN, Buzdar AU, Smith TL, Fraschini G. Clinical course of breast cancer patients with liver metastases. *J Clin Oncol* 1987; **5**:773–782.

3 Hoe AI, Royle GT, Taylor I. Breast liver metastases—incidence, prognosis and outcome. *J R Soc Med* 1991; **84**:714–716.

4 Hortobagyi GN. Overview of treatment results with trastuzumab (Herceptin) in metastatic breast cancer. *Semin Oncol* 2001; **28**(**6 suppl 18**):43–47.

5 McKeage K, Perry CM. Trastuzumab: a review of its use in the treatment of metastatic breast cancer overexpressing HER2. *Drugs* 2002; **62**:209–243.

6 Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, *et al.* Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002; **20**:719–726.

7 Baselga J. Clinical trials of single-agent trastuzumab (Herceptin). *Semin Oncol* 2000; **27**(**5 suppl 9**):20–26.

8 Takahashi M, Inoue K, Goto R, Tamura M, Taguchi K, Takahashi H, *et al.* Metastatic breast cancer of HER2 scored 2+ by IHC and HER2 gene amplification assayed by FISH has a good response to single agent therapy with trastuzumab: a case report. *Breast Cancer* 2003; **10**:170–174.

9 Rossi A, Colantuoni G, Cantore N, Panico L, DeChiara G, Ferbo U, *et al.* Complete response of severe symptomatic bone marrow metastases from heavily pretreated breast cancer with a 3-week trastuzumab schedule. A clinical case. *Anticancer Res* 2004; **24**:317–319.

10 Sawaki M, Ito Y, Tada K, Mizunuma N, Takahasi S, Horikoshi N, *et al.* Efficacy and safety of trastuzumab as a single agent in heavily pretreated patients with HER2/*neu*-overexpressing metastatic breast cancer. *Tumori* 2004; **90**:40–43.

11 Singletary KW, Frey RS, Yan W. Effect of ethanol on proliferation and estrogen receptor-alpha expression in human breast cancer cells. *Cancer Lett* 2001; **165**:131–137.

12 Fan S, Meng Q, Gao B, Grossmann J, Yadegari M, Goldberg ID, *et al.* Alcohol stimulates estrogen receptor signaling in human breast cancer cell lines. *Cancer Res* 2000; **60**:5635–5639.

13 Izevbigie EB, Ekunwe SI, Jordan J, Howard CB. Ethanol modulates the growth of human breast cancer cells *in vitro*. *Exp Biol Med* 2002; **227**: 260–265.

14 Meng Q, Gao B, Goldberg ID, Rosen EM, Fan S. Stimulation of cell invasion and migration by alcohol in breast cancer cells. *Biochem Biophys Res Commun* 2000; **273**:448–453.

15 Zhu Y, Lin H, Li Z, Wang M, Luo J. Modulation of expression of ribosomal protein L7a (rpL7a) by ethanol in human breast cancer cells. *Breast Cancer Res Treat* 2001; **69**:29–38.

16 Luo J, Miller MW. Ethanol enhances erbB-mediated migration of human breast cancer cells in culture. *Breast Cancer Res Treat* 2000; **63**:61–69.