Trastuzumab plus Estrogen Suppression as Salvage Treatment in a Case of Liver Failure Due to Metastatic Breast Cancer

ANDREA A. MARTONI, ALESSANDRA BERNARDI and SARA QUERCIA
Medical Oncology Unit, S. Orsola-Malpighi Hospital, Bologna, Italy

Abstract. Background: Liver failure associated with metastatic breast cancer is a short-term survival condition in which standard chemotherapy is almost always contraindicated. Case Report: A 45-year-old premenopausal woman with jaundice, due to extensive metastatic liver involvement from infiltrating ductal carcinoma of the right breast, with positive hormonal receptors (ER 70%, PgR 80%), a high proliferative index (Ki-67 60%) and HER2 overexpressed (immunohistochemical HercepTest 3+) was referred. Metastases were also present in the lymph nodes of the homolateral axilla and in both lungs (T2N2M1). Liver function indices were quite altered, in particular: total bilirubin 12.32 mg/dl (direct 11.49 mg/dl), ammonemia 270 µMoles/l and albumin 2.9 g/dl. Treatment consisted of trastuzumab at a loading dose of 4 mg/kg, followed by weekly doses of 2 mg/kg, Leuprolide at 3.75 mg intramuscularly monthly and Tamoxifen 20 mg daily. Results: The patient presented a rapid and progressive improvement in her clinical conditions and in liver tests. The jaundice was resolved after 1.5 months and after 4 months she had normal liver function tests and an objective partial response was evident. The treatment was optimally tolerated. At this point Taxol, at a dose of 80 mg/m2 weekly, was added. After 10 months, the patient was well with a very important objective remission of all the tumor masses, and is continuing with the combined treatment. Conclusion: Trastuzumab plus estrogen suppression can be an effective salvage therapy in patients with liver failure due to metastatic HER2 and ER/PgR-positive breast cancer.

The liver is a common site of metastases in breast cancer. Its presence has long been associated with a poor prognosis. In addition, the specific population of breast cancer patients presenting liver disease and associated liver dysfunction seems to have a poorer prognosis in comparison with other patients with liver metastases. As the most active cytotoxic agents in breast cancer have a significant hepatic metabolism and/or biliary excretion, these patients cannot receive standard chemotherapy owing to the high risk of life-threatening toxicity.

As such patients have commonly been excluded from clinical trials, there are currently no clear recommendations concerning the management of such dramatic presentations and often they are treated with an empirical dose reduction of active drugs, or else are definitively excluded from antitumor treatments.

In this report, we describe the case of a breast cancer patient, with extensive metastatic liver involvement with associated hepatic failure, in whom trastuzumab plus estrogen suppression has reversed the severe metabolic condition, in association with a rapid clinical improvement, allowing her to undertake standard cytotoxic chemotherapy.

Case Report

On February 2005, a 45-year-old woman was referred to us as she had been suffering from jaundice due to extensive metastatic liver involvement with a nodule in the right breast, shown by biopsy to have an infiltrating cancer. She had no familial history of breast cancer, nor any prior significant history of other diseases. She had had one pregnancy at the age of 24 and regularly menstruated. Her recent history began in December 2004, when progressive jaundice accompanied by fever and a persistent cough appeared. She was found to have a painful liver enlargement and a nodule in the right breast. Mammography and echography showed a pathological area larger than 2 cm in diameter at the inferior-out quadrant of the right breast.

The true-cut biopsy had showed an infiltrating ductal carcinoma, with positive hormonal receptors (ER 70%, PgR 80%), high proliferative index (Ki-67 60%) and overexpressed HER2 (immunohistochemical HercepTest DAKO 3+). CT and ultrasound scan of the abdomen had shown a marked liver enlargement with a completely altered structure because of numerous secondary lesions, without significant biliary stasis (Figure 3A). In addition, the CT scan of the thorax had

Correspondence to: Andrea Angelo Martoni, MD, Medical Oncology Unit, S. Orsola-Malpighi Hospital, via Albertoni 15, 40138 Bologna, Italy. e-mail: martoni@aosp.bo.it

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shown multiple small (diameter <1 cm) bilateral pulmonary lesions. At the first evaluation, the patient had a Karnofsky performance status (KPS) of 60; she complained of marked asthenia, anorexia, dyspnoea, cough and pain on the right side of the abdomen. On physical examination, jaundice was manifest; the abdomen was enlarged and a voluminous hepatomegaly was palpable with the liver edge at 13 cm from costal arch. At the inferior-outer quadrant of the right breast, a thickened area of 5 cm x 4 cm was palpable; the underlying skin was partially retracted with “peau d’orange” appearance. An enlarged 2-cm lymph node was palpable in the homolateral axilla. On February 5, 2005, the blood chemistry test showed: total bilirubin 12.32 mg/dl (direct 11.49 mg/dl and indirect 0.83 mg/dl), sGOT 814 U/ml, sGPT 216 U/ml, alkaline phosphatase 3338 U/l, gamma GT 3266 U/l, ammonemia 270 ÌMoles/l (normal values 11-35), albumin 2.9 g/dl, WBC 27,290/ÌL (72% neutrophils), Hb 14.3 g/dl and platelets 392,000/Ìl. The tumor marker blood levels were: CEA 39.2 ng/ml and CA 15.3>4000 U/ml. A bone scan was negative for metastases.

Beginning on February 8, 2005, an intravenous (i.v.) infusion of trastuzumab (T) at a loading dose of 4 mg/kg was started and continued with 2 mg/kg weekly doses until the time of drafting the present report. Hormonal therapy with the LHRH analogue, leuprolide, at the dose of 3.75 mg intramuscularly (i.m.) monthly was started on February 7, and has continued until the present. Tamoxifen (TAM) at 20 mg daily was associated with the LHRH analogue.

Results

The patient presented a rapid and progressive improvement in her clinical condition. Table I shows the progressive improvement in the liver function tests during treatment with T and hormonal therapy. Jaundice was resolved 44 days after the beginning of the therapy and, in parallel, the tumor marker levels also progressively decreased (Figures 1 and 2). By April 20, 71 days after the start of T-therapy, she felt well, was symptom-free, with KPS 100; upon physical examination, the breast nodule was 3 cm x 2 cm and no lymph node was palpable in the axilla. The CT scan showed a marked reduction in the number and size of lung metastases, and a normalization of the liver volume, with persistence of multiple lesions diffuse throughout the whole liver (Figure 3B). By May 12, all the blood chemistry tests were within the normal range. Consequently, on May 19, Taxol was added to T + LHRH analogue treatment, at a dose of 80 mg/m2 weekly. This treatment has been continued up to December 2005. The CT scans on July and November 2005, showed the absence of certain lung metastases and the progressive change in the liver structure because of the presence of multiple hypodense images prevalently of thin and linear but also pseudo-nodular appearance associated with aspects of liver parenchyma fibrosis (Figure 3C and 3D). At the time of writing, upon physical examination only a slight thickening is palpable in the right breast with a normalization of the surrounding skin and the liver edge palpable at the costal arc. The tumor marker levels are: CEA 1.2 ng/ml and CA 15.3 23 U/ml. The patient is continuing with the treatment.

Discussion

Liver metastases from breast cancer are present in about 20% of patients at the time of the diagnosis of metastatic disease. In a series of 233 cases with liver metastases treated in the period 1973-1980 at the M. D. Anderson Hospital and Tumor Institute in Houston, U.S.A., 15% were at the initial diagnosis (stage IV breast cancer) (1). With disease advancement, the incidence of liver metastases increases to about 50% of patients. For years it has been believed that such a localisation was constantly associated with a severe progression from the prognostic standpoint. With the use of modern chemotherapy and, in particular, agents, such as anthracyclines, taxanes and vinorelbine, the chances of obtaining an objective remission of the disease, as well as survival, no longer appear to be lower than that of the cases bearing metastases in other sites. Actually, even above average survival has been described for patients with metastases isolated to the liver (2). In this type of patient, besides systemic medical treatment, surgical resection (3), thermo/cryo-abilation (4), or even intra-arterial chemotherapy (5) may be worthwhile. The improvement in the results is the consequence not only of the development of

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<th>Table I. Liver function indices during treatment with trastuzumab and estrogen suppressive therapy.</th>
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Figure 1. CEA changes during treatment with trastuzumab and hormonal therapy.

Figure 2. CA 15.3 changes during treatment with trastuzumab and hormonal therapy.
the therapies, but also of a better knowledge of the natural history of the disease and the enhanced diagnostic capacities, that now allow us to detect the presence of small and numerically-limited liver metastases, unlike in the past.

However, the patient in whom the liver metastases are associated with alterations in functionality, and, in particular, in whom jaundice is present, has an even more severe prognosis. Indeed, the three categories of drugs mentioned above are prevalently metabolised at the hepatic level and eliminated by the biliary route. As a consequence, those patients with alterations in their hepatic function are systematically excluded from the clinical trials. A recent review of the literature has dealt with the treatment of the patients with liver metastases and functional alterations (6). The association between hepatic metastases and jaundice is not a frequent case of breast carcinoma and its incidence is not well defined in the literature.

In the series of patients with liver metastases from the M.D. Anderson Hospital, values of bilirubin >1.5 mg/dl were observed in 12% of the cases (1). Jaundice is more often associated with a diffuse spreading of the disease in the organ and generally appears in the course of the evolution of the disease. The therapeutic options for such patients are very limited and, in clinical practice, individualized choices are made on the grounds of the level of liver insufficiency. These range from the use of an anthracycline, such as low-weekly epirubicin (7), to reduced doses of mitoxantrone (8) or vinorelbine (9), or the use of drugs with absent or scarce elimination by the biliary pathway, such as cisplatin (9) and capecitabine (10), up to, as in the most serious cases, not administering chemotherapy, but limiting the treatment to the best supportive therapy (6).

Faced with patients with liver metastases in whom the tumour shows positive ER and/or PgR, hormonal therapy can have an important therapeutic contribution, if combined with chemotherapy and, in selected cases, even as a single therapy. However, in the case of extensive hepatic involvement,
especially if associated with functional insufficiency, its therapeutic role appears to be marginal, at best (1).

T is a humanized murine monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). In the tumors that hyperexpress HER2, T is capable of inducing an objective remission in 26% of the non-pre-treated cases (11) and in 15% of the pre-treated cases (12). In association with chemotherapy, it has proven to be capable of increasing the time to progression and survival as compared to chemotherapy alone when used as front-line therapy (13, 14), irrespective of the site of the metastases. In these trials, however, the patients with elevated bilirubin levels were excluded. While pharmacokinetic data suggest that the disposition of T is not altered on the basis of age or serum creatinine up to 2.0 mg/dl, no data are available on T disposition and altered liver function.

The current case report brings up two main considerations: the first concerns the description of a new therapeutic option for a subset of patients with short-term survival, and the latter, more general, the therapeutic potential of combining T with hormonal manipulations.

Upon presentation, our patient had such a diffuse involvement of the liver with severe alteration of functional indices that in the pre-trastuzumab era no chance of clinical usefulness could have been attributed to cytotoxic chemotherapy, and only a symptomatic approach would have been justified. Even if the literature had been lacking data on the pharmacokinetics of T in the liver-failure condition, on the basis of the biological characteristics of the tumor (overexpression of HER2 and positive ER and PgR), we decided to start T plus hormonal treatment as a salvage therapy. As the patient was pre-menopausal, hormonal treatment consisted of LHRH analogue administration plus TAM. The treatment induced a rapid and progressive improvement in her clinical status so that total bilirubin reached the normal range 1.5 months after the start of therapy, and a partial objective response was evident after 2.5 months. These results subsequently prompted us to associate treatment with weekly Taxol. At the time of the present report (10 months from the diagnosis), she is still receiving treatment, feeling well, with a normal liver function, showing an optimal partial disease remission.

The second consideration that the case suggests concerns the role of a T plus hormonal therapy combination in patients with HER2 and ER/PgR-positive tumors. Indeed, while the value of the combination of T with chemotherapy in the tumors that overexpress HER-2 is by now well-proven, less clear-cut is the role of the combination of T with hormone therapy when hormonal receptors are also expressed in the tumor (15). Although there is an inverse relationship between HER2 overexpression and the quantitative ER status (1), overall about 50% of the HER2-overexpressing breast cancer cases are ER- and/or PgR-positive. While T is effective in HER2-positive tumors regardless of the ER status, sensitivity to hormonal therapy can be negatively conditioned by an overexpression of HER2. Pre-clinical and clinical data indicate that HER2 is associated with a poor response to TAM in ER and/or PgR-positive breast cancer (17, 18). There is evidence that this is caused by "crosstalk" between the HER2 and ER intracellular signaling pathways, and that HER2 signaling stimulates the agonistic estrogenic proliferative effect of TAM (19, 20). This does not occur where the hormonal therapy is represented by aromatase inhibitors as confirmed by their superiority over TAM in the neoadjuvant therapy of post-menopausal patients with ER and HER2 positive breast cancer (21-23).

Data on the antitumor effect of ovarian ablation in pre-menopausal patients with HER2 overexpressing advanced breast cancer are lacking. However in the adjuvant setting, HER2 overexpression is not reported adversely, and it may favorably influence the response to adjuvant oophorectomy and TAM treatment in patients with ER-positive tumors (24).

The addition of T to the hormonal therapy has, until now, been studied little. In the pre-clinical field, the addition of T to TAM has produced contrasting results as it has been reported not only to reverse the resistance to TAM (25) but also the opposite (26). The combination of T with aromatase inhibitors has given interesting results in a small study on 26 patients (27) and at present two randomized studies are in progress involving anastrozole and letrozole in association with T in post-menopausal patients with HER2 and ER/PgR positive metastatic breast carcinoma (15). This case report draws our attention to the therapeutic potential of the combination of T and a hormonal manipulation as an effective treatment schedule even without the concomitant administration of chemotherapy.

In conclusion, the present case report demonstrates that T now allows us to deal with and to be able to reverse the short-term survival-associated clinical condition, such as that of liver metastases with severe functional failure, when the tumor overexpresses HER2. The concomitant presence of ER and PgR allows us to associate an estrogen-suppressive treatment that has to be appropriate to the menopausal status. This combined treatment represents a new safe therapeutic option for this small subset of patients with a very poor prognosis. Its favorable effect also subsequently allows association with a T-synergistic cytotoxic agent, such as Taxol, previously not administrable owing to the liver insufficiency.

References


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