Excellent Biochemical Response to Polychemotherapy with Nab-Paclitaxel/Gemcitabine in an 82-Year-Old Female with Metastatic Breast Cancer

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Key Words
Metastatic breast cancer · Liver metastases · Bone metastases · Chemotherapy · Elevated bilirubin levels · Nab-paclitaxel

Abstract
We report the case of an 82-year-old female diagnosed with HER2-negative, hormone receptor (HR)-positive metastatic breast cancer. Upon biochemical disease progression of the initially HR-receptor positive disease under anti-hormonal treatment with tamoxifen and letrozole, she received combination chemotherapy with paclitaxel/gemcitabine. Due to her suffering from severe toxicity, therapy was switched to nab-paclitaxel/gemcitabine. From April 22, 2013, to July 15, 2013, the patient received 5 cycles of nab-paclitaxel/gemcitabine as a 30-min infusion every 3 weeks, with excellent biochemical responses to treatment. Tumor marker levels as well as bilirubin were reduced to baseline levels. Chemotherapy with nab-paclitaxel/gemcitabine was well tolerated. At a follow-up visit immediately after the end of chemotherapy, the patient reported well-being and presented with a Karnofsky performance status (KPS) of 100%. At the last follow-up in October 2013, she was alive with multiple metastatic sites in the liver and bone metastases in the spine without risk of fracture and a KPS of 90%. She has received palliative single agent chemotherapy with capecitabine (14/7 regimen, 1,500 mg b.i.d.) since August 2013 and continued to show a good biochemical treatment response at the last follow-up in October 2013. Since August 2013, the patient has also received denosumab (120 mg sc, q4w) for her metastatic bone disease. As of July 2014, treatment has not been changed and the patient reports her well-being.
Introduction

Stage IV breast cancer (metastatic breast cancer, MBC) is still an incurable disease with a median 5-year overall survival rate of 25% [1]. However, this figure does not reflect the broad range of different courses of MBC with patients surviving only a few months, and others having a chronic disease for many years. The most important treatment issues in patients with MBC are to control the disease and its symptoms and to maintain the patients’ quality of life as long as possible. There are many treatment options for patients in the metastatic setting. To select the appropriate therapy, the individual patient and the special situation of her illness as well as her personal wishes must be respected. In elderly patients, comorbidities and performance status influence the available and feasible treatment possibilities.

Endocrine therapy alone is the first therapy of choice for patients with hormone receptor-positive, HER2-negative MBC. After the failure of anti-hormonal agents (anti-estrogens, aromatase inhibitors) and/or rapid progression of existing metastases or new metastatic sites, either single-agent or combination chemotherapy is recommended. The choice of treatment depends on the aggressiveness of the disease, metastatic sites and individual factors such as age, comorbidities and performance status of the patient. In this palliative setting, chemotherapy remains the mainstay of treatment.

Apart from disease control, one crucial treatment goal in this non-curative setting must be maintaining the patient’s quality of life. Anthracyclines and/or taxanes are recommended agents for first-line treatment. A new treatment option is nab-paclitaxel (nanoparticle albumin-bound paclitaxel). Although it is currently approved for second-line treatment after the failure of anthracycline-based chemotherapy [2], nab-paclitaxel can also be a possible therapeutic approach in first-line treatment, especially in a weekly schedule [3].

Albumin-bound paclitaxel with a mean particle size of 130 nm has significant practical advantages compared to solvent-based taxanes. It can be administered without antiallergic premedication and shows favorable linear pharmacokinetic characteristics. With albumin as the transport protein for the cytotoxic agent, albumin-specific pathways and mechanisms are used for nab-paclitaxel to gain access to the tumor interstitium [4–6].

Case Report

An 82-year-old woman was diagnosed with an invasive ductal adenocarcinoma of the left breast in November 2012. TNM classification was cT4 cN1 M1 (hep). The tumor was well differentiated (G2), hormone receptor positive (OR 95%, PR 30%) and HER2 negative. The patient received antihormonal treatment with the antiestrogen tamoxifen 20 mg (once/day) from November 21, 2012, until February 5, 2013. While bilirubin levels remained low during that period (1.0 mg/dl at baseline, 0.8 mg/dl on February 5, 2013), tumor marker levels of CA 15–3 and CEA increased from 1,068 U/ml (CA 15–3) and 13.9 ng/ml (CEA) to 2,779 U/ml and 43.5 ng/ml, respectively. Due to this biochemical disease, progression therapy was switched to the nonsteroidal aromatase-inhibitor letrozole on February 5, 2013, upon which tumor marker levels continued to rise and bilirubin levels doubled, indicating a resistance to the antihormonal treatment and active growing process in the liver. Therefore, letrozole was discontinued and a taxane-based combination chemotherapy was started.

The first course of chemotherapy consisting of gemcitabine 1,000 mg/m² and paclitaxel 200 mg/m² was administered on March 18, 2013. No response was observed, but progressive disease with a remarkable surge in tumor marker and bilirubin levels with a peak of
6,982 U/ml in CA 15–3 levels, 127.6 ng/ml in CEA levels and 13.1 mg/dl in bilirubin levels on April 3, 2013. The patient developed a severe mucositis from March 28 until April 11. The oral symptoms made swallowing and, as a consequence, eating and drinking extremely painful, and her quality of life was dramatically reduced. Due to the progression of the disease and the painful mucositis, we stopped the treatment with paclitaxel/gemcitabine.

On April 22, 2013, after the severe mucositis had disappeared and symptoms had receded, we started a new therapy with nab-paclitaxel 200 mg/m² and gemcitabine 1,000 mg/m² every 3 weeks. On April 11, tumor marker and bilirubin levels had gone to 4,232 U/ml (CA 15–3), 74.3 ng/ml (CEA) and 3.8 mg/dl (bilirubin) and continued to decline during the 5 further cycles of nab-paclitaxel/gemcitabine. Treatment with nab-paclitaxel/gemcitabine was tolerated well, with no severe toxicity, and especially no neurotoxicity was observed. On June 24, 2013, the CA 15–3 level was reduced to 947 U/ml, the CEA level to 12.7 ng/ml, and the bilirubin level was at 0.7 mg/dl. All biochemical parameters were below baseline. Due to the patient’s excellent tolerance of the applied dose of 200 mg/m² nab-paclitaxel in combination with gemcitabine, the nab-paclitaxel dosage was escalated to 300 mg/m² on June 24, 2013, for the 4th cycle of chemotherapy. By July 15, 2013, bilirubin levels had been reduced even further to 0.5 mg/dl, CA 15–3 level was at 770 U/ml, and CEA level was 14.3 ng/ml (see table 1). On July 15, the patient received the last cycle of nab-paclitaxel/gemcitabine, and treatment was still tolerated well, without any neurotoxicity. On a follow-up visit on July 19, 2013, the patient reported her well-being and presented with a Karnofsky performance status (KPS) of 100%. She had no edema and no palpable enlarged lymph nodes.

Restaging examinations at the end of July showed a stable disease of the known primary tumor, and the liver metastases revealed multiple small ossary metastases in the spine as well as in the os sacrum and os ilium. A restaging CT performed on July 22, 2013, showed multiple liver metastases with partly irregular borders (multiple metastatic sites in the liver) in all segments and multiple small bone metastases in the spine without discernible fracture risk. A restaging mammography performed on July 22, 2013, showed the tumor in the left breast (BI-RADS assessment category 5) without infiltrations in the chest wall and axilla. A bone scan performed on July 29, 2013, revealed 3 vertebrae in need of further assessment upon which an MRI scan was done on August 5, 2013. It showed the same metastatic sites in the thoracic and lower spine without any risk of fracture or further damaging the existing fractures. Therapy with nab-paclitaxel had stabilized tumor and metastases, and disease symptoms were well controlled. On August 27, 2013, the patient was started on single-agent chemotherapy with capecitabine (14/7 regimen, 1,500 mg b.i.d.) and denosumab 120 mg s.c. every 4 weeks as well as calcium and vitamin D for the metastatic bone disease.

Restaging with various imaging modalities on October 22, 2013, showed stable disease of the tumor in the breast as well as of all metastatic sites: an upper abdominal ultrasound scan showed no enlarged lymph nodes and no relevant changes compared to the abdominal scan performed in July. Her breast ultrasound confirmed the known tumor in the left breast without enlarged or pathologic lymph nodes in the left axilla. Chest and abdominal CT scans showed no pulmonary metastases and confirmed stable disease of the liver metastases. No involvement of the left axilla was observed. Ossary metastases were reported to be stable without fractures or larger osteolysis.

Biochemical response to treatment was good with bilirubin levels remaining at 0.7 mg/dl. Tumor marker levels of CA 15–3 were reduced to 280 U/ml. At a follow-up visit, the patient presented with a KPS of 90% and reported a subjective well-being.

As of July 2014, the patient still receives capecitabine and denosumab and continues to show stable disease.
Discussion

In Germany, nab-paclitaxel is currently approved for the treatment of MBC after failure of first-line chemotherapy and for whom anthracycline-containing chemotherapy is not indicated [7]. Relevant to everyday clinical practice is the more favorable safety profile of nab-paclitaxel compared to the solvent-based, conventional paclitaxel [8]. Maintaining the patient’s quality of life is crucial in the metastatic, non-curative setting. Since our patient developed severe mucositis and wanted to discontinue chemotherapy, good tolerability was one of the main aspects in the choice of the subsequent chemotherapy. Roy et al. [9] reported significant antitumor activity and a favorable toxicity profile of weekly nab-paclitaxel/gemcitabine in 50 previously untreated patients with MBC. Although our patient was pretreated with conventional paclitaxel with considerable mucosal toxicity, we observed an excellent tolerability of nab-paclitaxel/gemcitabine as well as a considerable efficacy in our patient. Excellent biochemical response was achieved with all parameters reverting to levels below base line. Remarkably, the 82-year-old patient presented with a KPS of 100% after the end of all 5 cycles of nab-paclitaxel/gemcitabine.

Despite metastatic disease in the liver and elevated bilirubin levels, treatment with nab-paclitaxel/gemcitabine was very well tolerated and no neuropathy or recurrent mucositis was observed. Our findings suggest that patients with elevated bilirubin up to 10 mg/ml can be safely treated with nab-paclitaxel/gemcitabine with the initially reduced nab-paclitaxel dosage being escalated in the course of the treatment.

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### Table 1. Bilirubin- and tumor marker levels during anti-hormonal treatment and chemotherapy

|                          | CA 15-3 (U/ml) | CEA (ng/ml) | Bilirubin (mg/dl) |
|--------------------------|----------------|-------------|-------------------|
| Tamoxifen
  November 29, 2012    | 1,068          | 13.9        | 1.0               |
  January 22, 2013        | 2,102          | 31.4        | 0.7               |
| Letrozole
  March 6, 2013         | 4,121          | 82.5        | 2.0               |
| Paclitaxel/gemcitabine  |
  April 3, 2013           | 6,982          | 127.6       | 13.1              |
| Nab-paclitaxel/gemcitabine
  April 22, 2013          | 3,694          | 48.3        | 1.6               |
  May 13, 2013             | 1,651          | 23.8        | 0.9               |
  June 3, 2013             | 1,259          | 15.8        | 0.9               |
  July 15, 2013            | 770            | 14.3        | 0.5               |