

Long-term Control of Bone Marrow Carcinosis and Severe Thrombocytopenia with Standard-dose Chemotherapy in a Breast Cancer Patient: A Case Report

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Abstract. *Background:* Primary metastatic breast cancer with bone marrow involvement and pronounced thrombocytopenia is rare. The myelosuppressive effect of most cytotoxic drugs limits chemotherapy in patients with cytopenia due to marrow involvement. *Case Report:* A 62-year-old patient, who presented with locally and systemically advanced breast cancer, is reported. The initial work-up revealed bone marrow carcinosis with thrombocytopenia of less than 20,000/mm³, lung and osseous metastases without signs of suppressed erythropoiesis and leucopoiesis. The patient was stabilized with 6 different standard-dose chemotherapy regimens, antihormonal therapy, and trastuzumab before dying 57 months after first diagnosis. The patient received only platelet transfusions on 2 instances with platelets of 2,000/mm³. *Conclusion:* This case illustrates that aggressive standard chemotherapy may be feasible in selected patients with bone marrow carcinosis-associated thrombocytopenia without major bleeding episodes.

Advanced breast cancer remains an incurable disease and has a poor prognosis. The aim of treatment is palliative with emphasis on the quality of life and possibly prolongation of survival. The medical approach to the management of metastatic breast cancer now includes new cytotoxic and hormonal agents as well as monoclonal antibodies. Endocrine therapy is the initial treatment for postmenopausal women diagnosed with metastatic disease if the tumor is both ER- and PR-positive (1).

If the disease does not respond, cytotoxic therapy can be considered (2-6, 9). A clinical benefit for patients with

metastatic breast cancer is possible even after several preceding cytostatic therapies (2).

Primary metastatic breast cancer with bone marrow involvement and pronounced thrombocytopenia at the time of diagnosis of breast cancer is very rare.

Case Report

A 62-year-old patient presented with primary exulcerated, invasive ductal, G3, hormone receptor-positive breast cancer. Hematological examination revealed a white blood cell (WBC) count of $7.4 \times 10^3/\text{mm}^3$ with 77% granulocytes, 19.5% lymphocytes and 2.6% monocytes, a hemoglobin of 11.6 g/dl and RBC of $4.77 \times 10^6/\text{mm}^3$ and a low platelet count of only 15,000/mm³. The initial work-up revealed bone marrow carcinosis and lung and osseous metastases. Bone marrow metastasis was documented by bone marrow biopsy (Figure 1). No signs of suppressed erythropoiesis or leucopoiesis were present. The peripheral blood smear showed no platelet aggregation, which would suggest pseudothrombocytopenia, or fragmented red blood cell (RBC), which would suggest underlying chronic disseminated intravascular coagulopathy.

The CT scan of the abdomen showed no liver metastases or splenomegaly. The patient was started on tamoxifen initially. There was no response, thus cytotoxic therapy was initiated. During the 57 months of follow-up, the patient received a total of 6 sequential cytotoxic regimens. The dosages used in these regimens, listed in Table I, were those recommended by available randomized phase III or phase II studies for patients with adequate bone marrow function. For example, the patient received 4 cycles of doxorubicin 75 mg/m^2 and docetaxel 75 mg/m^2 , both administered on day 1, 10 cycles of capecitabine monotherapy and 6 cycles of CMF. During a few chemotherapy cycles, the patient received granulocyte colony stimulating factors. Grade 3 and 4 neutropenia and leucopenia occurred on more than 10 occasions, but the patient never experienced febrile

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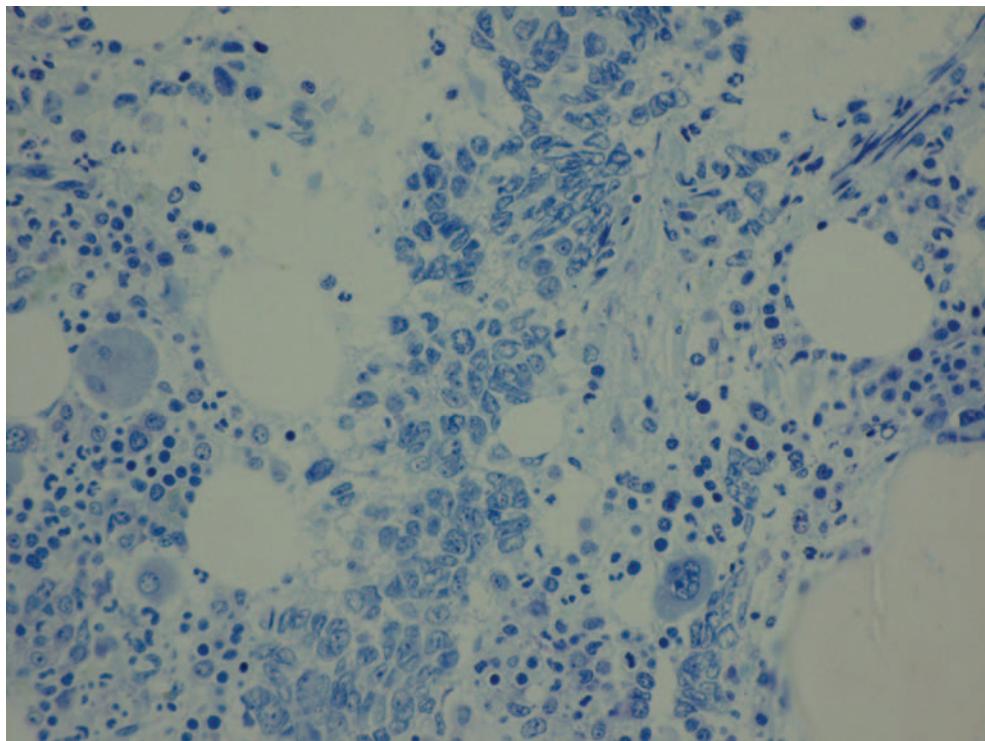


Figure 1. Bone marrow infiltration with tumor cells without signs of hematopoietic suppression documented by pretherapeutic bone marrow biopsy.

neutropenia. Grade 1 anemia was often observed, too. Once clinically tumor growth had been stabilized, the patient was treated with exemestane. The subsequent progression was treated with 8 cycles of vinorelbine, 11 cycles of gemcitabine 1000 mg/m² on days 1 and 8 and 4 cycles of carboplatin AUC 5 (Table I). The Her-2-neu status became available 34 months after first diagnosis and the patient was then treated with trastuzumab in addition to chemotherapy. From the start of antitumor therapy the patient received additional pamidronate monthly due to bone metastases. Because of severe bleeding from tumor exulceration of the breast, the patient underwent palliative partial resection of the left breast 34 months after first diagnosis. In the last 4 months of her disease, the patient developed extensive metastases in the left orbital area and progression at all previous metastatic sites. At that time, palliative radiotherapy and antihormone therapy with toremifene were initiated without success. The patient died of disease 57 months after first diagnosis.

The platelet counts during the course of the disease are listed in Table I and Figure 2. There were no clinical signs of major bleeding, despite platelet levels of less than 20,000/mm³ over several months (Figure 2). Only at 2 nadirs, with thrombocytopenia of 2,000/mm³, did the patient develop facial petechiae and received 1 platelet transfusion each time.

The highest platelet count (148,000/mm³) (Table I, Figure 2) occurred shortly after the initiation of trastuzumab therapy. Interestingly, no clear correlation between the improvement of platelet counts and the tumor response or performance status was found during treatment.

At the time of first diagnosis, the tumor markers CEA and CA-15/3 had been elevated, but during the course of treatment they did not show any correlation with the clinical extent of the disease, the performance status, or the platelet counts. During almost all phases of therapy, the performance status was quite acceptable (Table I, column 3).

Discussion

The patient described here survived for 57 months after diagnosis of metastatic breast cancer with severe thrombocytopenia due to bone marrow carcinosis.

The literature contains few descriptions of cytotoxic therapy in patients with thrombocytopenia due to bone marrow metastases of breast cancer (3-6). In 1997, tamoxifen was the accepted gold-standard first-line treatment for advanced breast cancer in postmenopausal hormone receptor-positive women at the time of the first diagnosis (1). Because of the insufficient response to tamoxifen, the next step was the administration of cytotoxic chemotherapy (2-6). The rationale

Table I. Main events in the clinical course of disease of a 62-year-old patient with primary breast cancer metastatic to the bone marrow and significant thrombocytopenia.

Time after first diagnosis	Clinical tumor manifestation	Therapy	Response to treatment	Karnofsky index	Platelets /mm ³
0 months	Primary exulcerated, invasive ductal breast cancer on the left side, ER+/PR+, Her-2-neu +++, bone marrow carcinosis, osseous metastases	Start of tamoxifen therapy, pamidronate	NC	70	15,000
2 months	Clinical stabilization	Start of 4 cycles doxorubicin/docetaxel combination therapy	NC	70	33,000
6 months	Progression of osseous metastases	Start of 10 cycles capecitabine monotherapy	PR	70	12,000
14 months	Manifestation of exulceration of the breast	Start of 6 cycles of cyclophosphamide/methotrexate/5-Fluorouracil with sporadic administration of G-CSF	NC	80	18,000
20 months	Partial remission of breast exulceration	Start of exemestane consolidation therapy	PR	90	21,000
32 months	Metastases of the left sternoclavicular joint	Start of 8 cycles IV vinorelbine therapy	NC	90	16,000
34 months	Her-2 status available: Her-2-neu +++ in the primary *	Ongoing chemotherapy with vinorelbine, start of coadministration of trastuzumab therapy	PR	90	27,000
38 months	Bleeding from tumor exulceration of the breast	Palliative partial resection of the left breast		80	55,000
39 months	Sternum metastases	Start of 11 cycles gemcitabine + trastuzumab	NC	80	18,000
41 months	No clinical change	Ongoing gemcitabine + trastuzumab	NC	80	148,000
48 months	Metastases in osseous pelvis and the 5th lumbar vertebra	Start of 4 cycles of carboplatin + trastuzumab	NC	70	6,000
53 months	Left orbital metastases, progression at all previous metastatic sites	Start of toremifene therapy; palliative radiotherapy of the head, pelvis and the right knee	PG	70	9,000
57 months	Patient died at home from tumor progression	-	-	0	-

*The Her-2-neu status was available no earlier than 34 months after diagnosis.

NC - no change.

PG - progression.

PR - partial response.

was to exert a cytotoxic effect on tumor cells in the bone marrow and, thus, to favorably influence thrombopoiesis without compromising red and white blood stem cells, which had been normal during the early phases of therapy. We are well aware of the danger of bleeding due to thrombocytopenia (7), but we considered only 2 treatment options: to achieve a therapeutic response or control of bleeding by administering platelet transfusions. Elting *et al.* reported that the overall risk of bleeding in thrombocytopenic patients with solid tumors is low (7). The patient underwent sequential treatment with 6 different cytotoxic regimens which were administered at standard dosages (Table I, Figure 2).

In our patient, the best clinical antineoplastic effects were achieved with sequential capecitabine monotherapy, exemestane therapy, and gemcitabine/trastuzumab combination therapy, respectively (Table I). It is notable that exemestane led to a significant clinical response for 12

months after 2 standard cytotoxic regimens (doxorubicin/docetaxel and cyclophosphamide, methotrexate and 5-Fluorouracil) had failed (Table I). This finding supports recent data on the efficacy of aromatase inhibitors in hormone receptor-positive and Her-2-neu-positive disease (8). Trastuzumab was not available for our patient early in the treatment course. Even after 38 months of extensive therapy, the combination of trastuzumab and gemcitabine led to a clinically significant stabilization of the disease. Thus, it might be speculated that the earlier co-administration of chemotherapy or antihormonal therapy with trastuzumab might have even further favorably influenced the prognosis of our patient (8-10).

With the current knowledge of the treatment efficacy of selective aromatase inhibitors and trastuzumab, this combination would have been the treatment of choice in the described patient (7, 8, 11).

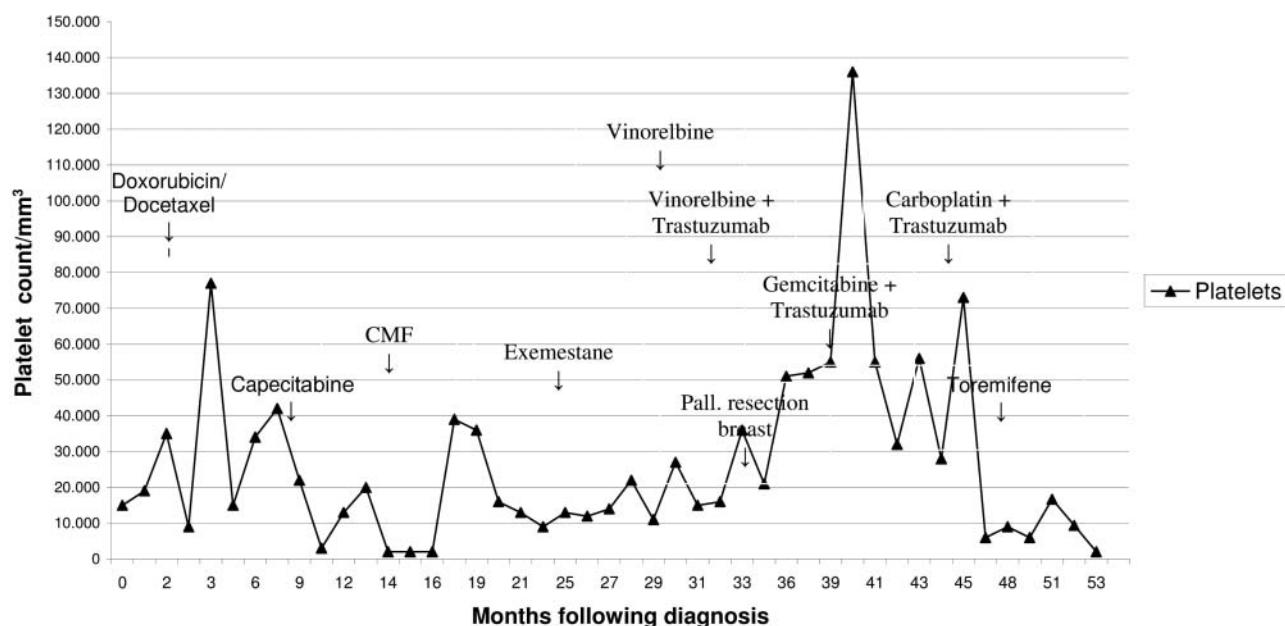


Figure 2. Course of platelet counts over 53 months of treatment in the patient with breast cancer and bone marrow carcinosis.

The efficacy of continuous chemotherapy over several years has also been documented (2-6). However, such therapy is very expensive and has not clearly demonstrated an advantage over interrupted therapy in the past.

In conclusion, this case illustrates that aggressive standard-dose chemotherapy might be feasible and beneficial in selected patients with bone marrow carcinosis-associated severe thrombocytopenia without major bleeding episodes. Furthermore, even very low platelet counts may be functionally sufficient to prevent bleeding in selected patients.

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