

Grade 4 Epistaxis in a Woman with Metastatic Breast Cancer Treated with Bevacizumab: A Case Report

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Abstract

We describe a 39-year-old woman with metastatic breast cancer who had grade 4 epistaxis induced by bevacizumab. The patient visited our outpatient clinic with complaints of a lump in her right breast, fatigue, dyspnea, abdominal distention, appetite loss, and weight loss of 10 kg over 1 year. Liver dysfunction was detected, with elevated levels of aspartate aminotransferase (271 IU/L), alanine aminotransferase (100 IU/L), alkaline phosphatase (4,205 IU/L), total bilirubin (2.7 mg/dL), and direct bilirubin (2.1 mg/dL). A secondary liver tumor that occupied most of the liver volume was found, and bone metastasis, ascites, and pleural effusion were also discovered. The Eastern Cooperative Oncology Group performance status was 2. A core needle biopsy of the right breast tumor revealed invasive ductal carcinoma of the breast (nuclear grade 1) that was positive for estrogen receptor and progesterone receptor and negative for human epidermal growth factor receptor 2 overexpression and had a high Ki-67 score. We chose combination chemotherapy with paclitaxel (80 mg/m² on days 1, 8, and 15) and bevacizumab (10 mg/kg on days 1 and 15) for 28 days (1 cycle). After completion of the first cycle of chemotherapy, the ascites and pleural effusion decreased, and the metastatic liver tumor shrank. The performance status improved from 2 to 1. On day 3 of the third cycle of chemotherapy, however, she began having persistent epistaxis. On day 6, she lost consciousness and was transported to the emergency room of our hospital. The hemoglobin level was 5.6 g/dL. Blood transfusion and endoscopic hemostasis were immediately started. Bevacizumab was discontinued, and paclitaxel alone was continued; after this change, epistaxis did not recur.

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Key words: bevacizumab, epistaxis, breast cancer, paclitaxel

Introduction

The aim of treatment in patients with metastatic

breast cancer is not to cure but to prolong survival while maintaining quality of life. Estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) are therapeutic targets of endocrine therapy

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Table 1 Laboratory findings before and after the start of the first cycle of combined chemotherapy with paclitaxel and bevacizumab

Variable (reference range)	Day 1	Day 8	Day 15
Aspartate aminotransferase, IU/L (10–28)	271	119	63
Alanine aminotransferase, IU/L (5–33)	100	74	41
Lactate dehydrogenase, IU/L (106–211)	827	621	379
Alkaline phosphatase, IU/L (104–338)	4,205	2,457	1,911
γ -Glutamyl transpeptidase, IU/L (10–30)	1,504	905	734
Total bilirubin, mg/dL (0.2–1.2)	2.7	1.7	1.1
Direct bilirubin, mg/dL (0.1–0.4)	2.1	1.2	0.9
C-reactive protein, mg/dL (<0.3)	5.71	3.49	0.65
White blood cells, $\times 10^2/\mu\text{L}$ (40–80)	6,900	1,000	5,900
Neutrophils, $\times 10^2/\mu\text{L}$	5,240	110	4,130
Red blood cells, $\times 10^4/\mu\text{L}$ (400–500)	454	433	421
Hemoglobin, g/dL (12–16)	14.7	13.9	13.2
Platelets, $\times 10^4/\mu\text{L}$ (20–40)	22.4	20.9	23.8

and anti-HER2 therapy, which are effective against metastatic breast cancer¹². On the other hand, there are no effective targeted drugs for HER2-negative and ER-negative breast cancer. In a recent study in patients with HER2-negative recurrent or metastatic breast cancer, combination therapy with paclitaxel and bevacizumab achieved significantly longer progression-free survival (PFS) than did paclitaxel alone^{3,4}. This combination therapy was approved for inoperable or recurrent breast cancer by the Japanese government in 2011. Increased PFS was also demonstrated with bevacizumab administered in combination with drugs other than paclitaxel^{15,6}.

An antiangiogenic biological agent, bevacizumab is a therapeutic antibody that specifically binds to vascular endothelial growth factor (VEGF), a potent proangiogenic factor^{7,8}. Both VEGF and its receptor are expressed in the majority of malignant tumors, including breast cancer⁹.

The side effects of bevacizumab include epistaxis, hypertension, inflammation of the nose, proteinuria, and intestinal bleeding^{3–6}. Epistaxis is the most common side effect but is usually mild and resolves spontaneously or after the nostrils are pinched. Here we report on a 39-year-old woman with metastatic breast cancer who had severe epistaxis caused by bevacizumab therapy.

Case Report

A 39-year-old woman (height, 161 cm; body weight,

44 kg) visited our outpatient clinic with complaints of a large lump in the right breast, fatigue, dyspnea, abdominal distention, appetite loss, and weight loss of 10 kg over 1 year. The lump had a maximal diameter of 4 cm and was accompanied by a skin ulcer. The bulbar conjunctiva was slightly yellowish. Her liver was enlarged and palpable over the upper abdomen. The Eastern Cooperative Oncology Group performance status (PS)¹⁰ was 2.

Laboratory tests revealed liver dysfunction, with elevated levels of aspartate aminotransferase (271 IU/L), alanine aminotransferase (100 IU/L), alkaline phosphatase (4,205 IU/L), total bilirubin (2.7 mg/dL), and direct bilirubin (2.1 mg/dL) (**Table 1**). Levels of carcinoembryonic antigen (204.8 ng/mL; reference range, <5 ng/mL) and CA15-3 (1,032.8 U/mL; reference range, 27.0 U/mL) were also elevated.

Computed tomography revealed a large mass in the right breast that had directly invaded the overlying skin and had metastasized to the regional lymph nodes, liver, and bone. Ascites and pleural effusion were also observed. The secondary liver tumor occupied most of the liver volume (**Fig. 1**).

Core needle biopsy of the mass revealed invasive ductal carcinoma of the breast (nuclear grade 1) that was positive for ER (80% of cells positive) and progesterone receptor (PgR; 60% of cells positive), negative for HER2 overexpression (HerceptTest [Dako Denmark A/S, Glostrup, Denmark], 1+), and had a high Ki-67 score (labeling index, 35%).

On the basis of these findings, we estimated that

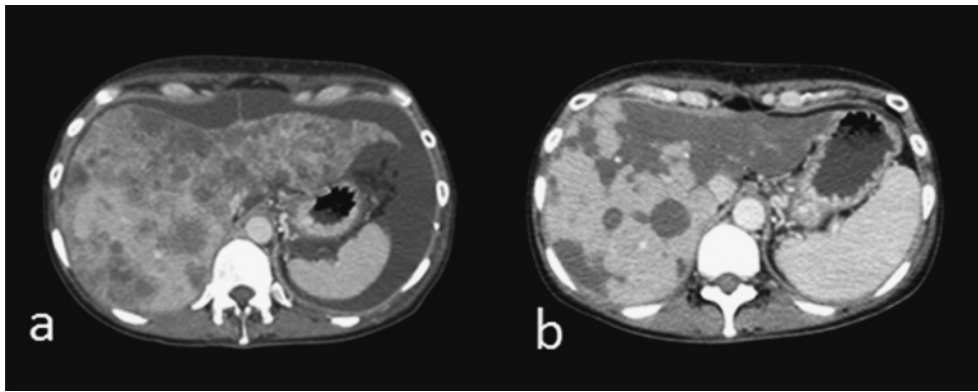


Fig. 1 Computed tomography reveals a secondary liver tumor accompanying the ascites and occupying most of the liver volume. After the first cycle of combination therapy with paclitaxel and bevacizumab, the liver tumor shrank and the volume of ascites decreased.

- a) Before chemotherapy
b) After the first cycle of chemotherapy

survival without treatment would be 1 or 2 months. We chose combination chemotherapy with paclitaxel (80 mg/m² on days 1, 8, and 15) and bevacizumab (10 mg/kg, on days 1 and 15) for 28 days (1 cycle). Before chemotherapy was started, the left-sided pleural effusion was drained to ameliorate dyspnea. Cytological analysis of the drained fluid revealed adenocarcinoma.

Liver function improved after the first round of chemotherapy; however, because of neutropenia (**Table 1**), the second cycle of chemotherapy was postponed, and the dose of paclitaxel was decreased. Computed tomography performed after completion of the first cycle of chemotherapy revealed decreased ascites and shrinkage of the secondary liver tumor (**Fig. 1**). The pleural effusion did not increase. The dyspnea resolved, and food intake increased as the patients regained her appetite. The PS improved from 2 to 1.

On day 3 of the third cycle of chemotherapy, however, the patient began having persistent epistaxis. On day 6, she lost consciousness and fell. She was transported to the emergency room of our hospital. The hemoglobin level was 5.6 g/dL. The epistaxis was assumed to be the cause of this episode, and blood transfusion and endoscopic hemostasis were immediately started. She recovered after this treatment.

Bevacizumab was subsequently discontinued, and

only paclitaxel was administered. In the 4 months since the episode, the epistaxis has not recurred.

Discussion

For patients with metastatic ER-positive breast cancer, endocrine therapy should be started and continued until life-threatening metastatic disease is observed. At this stage, the endocrine therapy should be replaced by chemotherapy. This strategy was proposed by Hortobagyi¹¹. In the present case, regardless of positivity for ER, chemotherapy was started instead of endocrine therapy because of the presence of life-threatening disease.

Paclitaxel in combination with bevacizumab significantly prolonged PFS compared with paclitaxel alone (11.3 vs. 5.8 months; hazard ratio, 0.48) in the E2100 trial³. In the JO19901 trial, the time to response was 3.6 months and the PFS was 13.6 months¹². Consequently, this combined therapy was considered effective because the therapeutic effects appeared quickly and the response was maintained for longer. These effects are mainly because of the properties of bevacizumab, which inhibits membrane and vascular permeability. Accordingly, ascites and pleural effusion are specifically controlled by combination therapy with bevacizumab. In our patient, the effects of treatment appeared quickly, and PS simultaneously improved.

In the E2100 trial, the combination of paclitaxel and bevacizumab resulted in higher quality-of-life scores than did paclitaxel alone¹³.

An unusual adverse effect of bevacizumab is epistaxis, which is reportedly observed in approximately 80% patients¹². In most patients, epistaxis is mild, does not require treatment, and starts before the fourth cycle¹². Epistaxis rated as grade 3 or 4 according to Common Terminology Criteria for Adverse Events version 4.0¹⁴ has been reported in 1.7% to 2.5% patients undergoing combination therapy with paclitaxel and bevacizumab^{4,12}. According to these criteria, grade 3 epistaxis indicates that transfusion or radiological, endoscopic, or surgical intervention is required, whereas grade 4 epistaxis indicates life-threatening consequences, necessitating urgent intervention. Because the present patient had grade 4 epistaxis, bevacizumab was immediately discontinued. We recommended that for all patients with grade 3 or 4 epistaxis bevacizumab should be discontinued and not readministered.

In conclusion, we have reported a rare case of grade 4 epistaxis caused by bevacizumab in a patient with metastatic breast cancer. Despite this severe adverse event, combination therapy with paclitaxel and bevacizumab was effective and quickly improved the PS.

Conflict of Interest: The authors declare no conflict of interest.

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