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CASE REPORT



Severe gastrointestinal hemorrhage during targeted therapy for advanced breast carcinoma

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ABSTRACT

The introduction of targeted agents has improved survival for patients with a number of types of cancer, including several breast cancer subtypes. However, these agents are not without toxicities, and the fact that many patients are now on targeted therapy for extended periods of time has presented new challenges for the management of adverse effects. Everolimus is an inhibitor of mTOR (the mammalian target of rapamycin) that is used as targeted therapy for advanced, hormone receptor–positive, HER2-negative breast cancer in postmenopausal women in combination with exemestane, after treatment failure with letrozole or anastrozole. Minor hemorrhagic events are relatively common with targeted agents, but life-threatening hemorrhages, although uncommon, can also occur. We report a case of life-threatening gastrointestinal bleeding in a 48-year-old woman being treated with everolimus for advanced infiltrating ductal carcinoma of the breast. The bleeding was successfully treated with 13 sessions of endoscopic hemostasis using argon plasma coagulation.

KEY WORDS

Gastrointestinal bleeding, everolimus, targeted therapy, argon plasma coagulation

1. INTRODUCTION

The introduction of targeted agents has increased survival for a number of types of cancer, including several breast cancer subtypes. However, these agents are not without toxicities, and the fact that most patients with breast cancer are now being treated continuously for longer periods of time means that management of toxicities can be challenging.

In July 2012, the U.S. Food and Drug Administration approved the use of everolimus, an inhibitor of mTOR (the mammalian target of rapamycin), in combination with exemestane, for the treatment of postmenopausal women with advanced hormone receptor–positive, HER2 (human epidermal growth factor receptor 2)–negative breast cancer after treatment with letrozole or anastrozole has failed[1]. The approval was based on the results of a multicentre randomized trial in 724 patients; safety was evaluated in 720 of the patients[1]. The approval listed the most common grades 3 and 4 adverse reactions as follows: stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis, and diarrhea. It indicated that participants in the trial had also experienced a number of grade 3 or 4 laboratory abnormalities, including lymphopenia, hyperglycemia, anemia, decreased potassium, increased aspartate aminotransferase, increased alanine aminotransferase, and thrombocytopenia. Adverse reactions were fatal in 2% of patients receiving everolimus and 0.4% of patients in the control group[1]. Of patients receiving everolimus, 24% had to permanently discontinue treatment because of adverse reactions (compared with 5% of patients receiving placebo)[1].

Here, we present a case of severe gastrointestinal bleeding during treatment with everolimus in a patient with breast cancer. Fujihara *et al.*[2] recently reported a case of life-threatening gastrointestinal bleeding that occurred during therapy with another mTOR inhibitor, temsirolimus, for advanced renal cell carcinoma. Clinicians have to be alert to the risk of severe gastrointestinal hemorrhaging with mTOR inhibitors so that they can respond quickly if such an event occurs in one of their patients.

2. CASE DESCRIPTION

Our patient, a 48-year-old woman, was diagnosed in June 2009 with a grade III infiltrating ductal carcinoma, which was estrogen receptor–positive, progesterone receptor–positive, and HER2-negative, with 2 of 14 lymph nodes being positive, staged T2N1M0 (IIB) initially. She underwent a bilateral mastectomy 1 month later and was treated with the FEC-D regimen

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(5-fluorouracil–epirubicin–cyclophosphamide followed by docetaxel) as adjuvant chemotherapy.

Follow-up revealed bone metastasis in September 2009. At that point, the patient's chemotherapy was changed to FEC-100 (100 mg/m^2 epirubicin, 500 mg/m^2 5-fluorouracil, and 500 mg/m^2 cyclophosphamide), and zoledronic acid was started. She was started on tamoxifen in January 2010.

One year later, computed tomography imaging showed metastasis to the liver. The patient was then started on docetaxel. In April 2011, further disease progression was found. The patient's chemotherapy was changed to vinorelbine, and her hormonotherapy was changed to letrozole and goserelin. After additional disease progression, she was started on albumin-bound paclitaxel in December 2011. She also started capecitabine, but developed some significant side effects associated with that drug; the dose therefore had to be decreased. She received her last treatment with capecitabine in June 2013.

In August 2013, everolimus (10 mg daily) with exemestane (25 mg daily) was started after evidence of disease progression, especially in the bones, was seen. The patient was anemic before that therapy started, but her anemia quickly worsened significantly, with her hemoglobin measuring 4.5 g/dL at 1 month after treatment initiation. She was admitted to hospital with worsening fatigue, pallor, melena, and hematochezia. She also exhibited thrombocytopenia and an increased partial thromboplastin time. Other coagulation tests were normal. She had not changed the dose of any of her medications and had not started or stopped any medications when started on targeted therapy.

Endoscopy (Figure 1) showed diffuse antral oozing, which resembled gastric antral vascular ectasia (GAVE). No ulcer was present, and the patient was not taking any nonsteroidal anti-inflammatory drugs.

Because the patient had a low platelet count, argon plasma coagulation was not performed initially; cyanoacrylate spray was used instead, with a successful result. Still, it was evident that the patient was continuing to bleed, because her hemoglobin remained below 8.0 g/dL even though she had received 8 units of packed red blood cells. She was admitted to the intensive care unit, started on pantoprazole, and transfused with platelets to maintain her platelet level above 50×10^9/L.

A new endoscopy showed multiple ulcerations in the antrum of the stomach. They were cauterized with argon plasma coagulation. Further endoscopy showed persistent oozing not from the ulcerations, but rather from the normal-looking mucosa. Cyanoacrylate spray and argon plasma coagulation were applied again.

No focal area of bleeding was observed. Bloodwork showed increased partial thromboplastin time and persistent thrombocytopenia, with a platelet count between 30 $\times10^9$/L and 50×10^9/L. Everolimus was now suspected to be the cause of the bleeding, because the patient had no underlying medical conditions associated with GAVE.

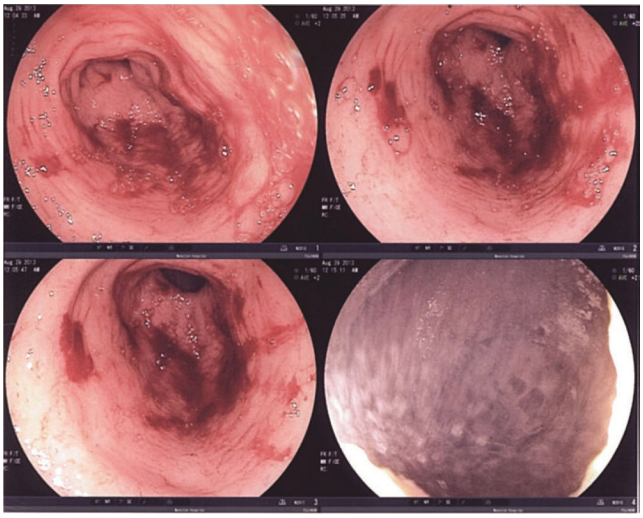


FIGURE 1 Esophagogastroduodenoscopy at the time of patient presentation with gastrointestinal bleeding shows diffuse mucosal oozing or bleeding with no obvious pathology (similar to what is seen in gastric antral vascular ectasia). The panels show four different views from the same localization.

Everolimus was stopped on September 23, 2013. Two weeks later, the oozing started to slow, and the patient's need for red cell transfusions was reduced. At this point, the patient required 1 transfusion each week (in September 2013, she had required 2–6 units of packed red blood cells daily). Her need for blood transfusions gradually declined with the hemostasis treatment. Treatment with a proton pump inhibitor had been started when the severe bleeding began, 1 month after the patient started taking everolimus. During the 2-month period of treatment for her bleeding, the patient received 13 sessions of endoscopic hemostasis and 52 units of transfused blood for severe anemia.

At 4 weeks after discontinuation of everolimus, the patient's symptoms had significantly improved (Figure 2), and she was discharged in good clinical condition 34 days after being admitted to hospital. The patient's gastric erythema and GAVE-like lesions had improved considerably 1 month after she was discharged from hospital.

3. DISCUSSION

Our patient's condition was consistent with GAVE, an uncommon cause of upper gastrointestinal bleeding. Associations have been reported between GAVE and a variety of conditions, most commonly autoimmune disorders[3]. Of the 45 patients in one case series, 28 (62%) had autoimmune or connective tissue disorders, most frequently Raynaud phenomenon (31%) and

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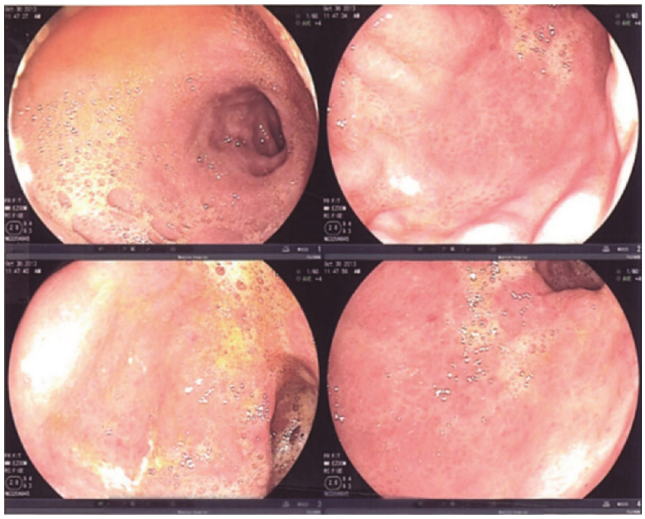


FIGURE 2 Esophagogastroduodenoscopy showing the antrum 37 days after discontinuation of everolimus.

sclerodactyly (20%)[4]. Approximately 30% of patients with GAVE have cirrhosis[3]. Among patients who present with GAVE without cirrhosis, 71% are women, with a median age of 73 years. Most of the patients with both cirrhosis and GAVE are men (75%), and their mean age is 65 years[5]. Gastric antral vascular ectasia has also been reported in patients undergoing chemotherapy after bone marrow transplantation[6].

Our patient had none of the comorbidities commonly associated with GAVE; however, we cannot rule out preexisting bleeding because esophagogastroduodenoscopy was not performed before treatment with everolimus was initiated. Endoscopic therapy is the preferred treatment for GAVE[7], and it proved to be successful in our patient.

Several completed trials have showed the benefits of a variety of targeted agents for treatment of advanced breast cancer[8]. One of those agents is everolimus, a derivative of sirolimus, which inhibits the MTOR pathway[9]. Severe bleeding events, although uncommon, have been known to occur with targeted therapies. A meta-analysis found that treatment with bevacizumab was associated with a 2.8% incidence of severe hemorrhagic events, with the risk being higher in patients with non-small-cell lung cancer, renal cell carcinoma, and colorectal cancer[10]. In a recent randomized controlled trial of the use of everolimus for advanced gastric cancer, 1 of the 439 patients in the everolimus arm of the study died because of severe gastrointestinal hemorrhage, and the death was suspected to be a result of study treatment[11]. A recent case report described a patient with gastrointestinal stromal tumours who was found to have GAVE 8 months after starting treatment with imatinib[12]. The mechanism by which therapy with MTOR inhibitors such as everolimus might result in GAVE is not yet clear.

4. SUMMARY

Life-threatening hemorrhagic events, although uncommon, must be considered a possible adverse effect of targeted therapy with MTOR inhibitors. Consequences could be grave for patients experiencing bleeding if their physicians continue to administer targeted therapies while they investigate other possible explanations for hemorrhagic events. In the present report, we described the development of GAVE in a patient being treated with the MTOR inhibitor everolimus for breast cancer. The patient's gastrointestinal bleeding was successfully treated with endoscopic hemostasis using argon plasma coagulation.

5. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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