Agranulocytosis Induced by Tamoxifen in a Breast Cancer Patient

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Established Facts

- Tamoxifen is the main adjuvant endocrine therapy for nonmenopausal patients with hormone-sensitive breast cancer.
- The toxicities of tamoxifen are mainly menopausal symptoms.
- Tamoxifen usually does not have hematological toxicities.

Novel Insights

- Tamoxifen can induce hematological toxicities.
- Tamoxifen can be responsible for agranulocytosis.

Keywords

Endocrine therapy · Tamoxifen · Agranulocytosis · Toxicity

Abstract

Background: The main side effects of tamoxifen are menopausal symptoms. We report a case of agranulocytosis induced by tamoxifen in a 33-year-old woman treated in the adjuvant setting. **Case Presentation:** Ten days after the beginning of tamoxifen treatment, the patient complained of asthenia and mucositis. Blood testing showed a grade 4 neutropenia (0.06 G/L) without any other major hematologic disorder. Tamoxifen was discontinued, and the patient received granulocyte colony-stimulating factor. Within 2 days, she recovered to a normal granulocyte count. Tamoxifen was then switched to the combination of ovarian suppression (trip-torelin) and aromatase inhibitor (anastrozole). **Conclusion:** Agranulocytosis is a very rare adverse event of tamoxifen.

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Introduction

Tamoxifen is the main adjuvant endocrine treatment for nonmenopausal patients [1]. The main side effects of this drug are menopausal symptoms such as hot flashes, vaginal discharge, venous thrombosis, joint pain, and bone loss [2]. Exceptionally, hematological toxicity has been reported. Here we describe a case of agranulocytosis induced by tamoxifen.

Case Report

A 33-year-old woman was diagnosed with an SBR grade 2, estrogen receptor-positive, progesterone receptor-negative, HER2-amplified, Ki-67 = 20%, invasive ductal carcinoma of the left breast. She had a total left mastectomy with axillary node dissection. The final tumor stage was pT1b N2a. She received adjuvant chemotherapy with 4 cycles of EC100 (epirubicin 100 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks) followed by 12 cy-

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Fig. 1. Bone marrow biopsy showing hypocellularity and pseudo-blockade of the granulocyte line at the promyelocyte stage and no mature granulocytes.

cles of weekly paclitaxel (80 mg/m²) and trastuzumab (2 mg/kg). She had grade 3 neutropenia after the first cycle of EC100. Then, she underwent radiotherapy (chest wall, infra- and supraclavicular area, and internal mammary nodes) and trastuzumab treatment (6 mg/kg, every 3 weeks). At the end of chemotherapy and radiation therapy, she had chemotherapy-induced amenorrhea. Thus, she received tamoxifen 20 mg/day [3, 4].

Ten days after the start of tamoxifen treatment, she came to the outpatient clinic for the 7th injection of every-3-week trastuzumab. She then complained of asthenia, as well as oral and anal mucositis. She had no fever. A complete biological assessment showed grade 1 anemia (11.5 g/dL), grade 1 leukopenia (1.5 G/L), grade 4 neutropenia (0.06 G/L), and no thrombocytopenia. Tamoxifen and trastuzumab were discontinued. A bone marrow biopsy was performed, showing hypocellularity with pseudoblockade of the granulocyte line at the promyelocyte stage and no mature granulocytes (Fig. 1). She received granulocyte colony-stimulating factor [5] in prophylaxis against febrile neutropenia and recovered to a normal neutrophil blood count after 2 days. Trastuzumab was reintroduced 10 weeks after the theoretical date. The endocrine treatment was switched to an aromatase inhibitor (anastrozole). Before 35 years of age, the rate of resumption of menstruation is high (91.7%) [6], which is why we added ovarian suppression (triptorelin) to the anastrozole treatment. There was no other episode of hematological toxicity.

Discussion

Hematological toxicity is very common with cytotoxic drugs, but non-chemotherapy-drug-induced agranulocytosis is a very rare adverse reaction [7, 8]. Initially, trastuzumab was suspected to be responsible for the agranulocytosis, since there was 1 reported case of grade 3 neutropenia induced by trastuzumab, potentially due to an immunological mechanism [9]. However, in our case, trastuzumab could be reintroduced after the neutrophil count had recovered, without any further hematological toxicity.

There are very few reported cases of tamoxifen hematological toxicity. In 2 reports, extended use of tamoxifen was responsible for global bone marrow suppression [10, 11]. In 1 report, agranulocytosis occurred in combination with fatal acute hepatic failure [12]. In the present case, a type II immune-mediated hypersensitivity reaction according to the Gell-Coombs classification was probably responsible for the agranulocytosis [13].

Statement of Ethics

The patient gave her consent for publication. This case analysis was approved by the scientific and ethics board of our medical center.

Disclosure Statement

Hugo Herrscher has no conflict of interest to declare. Julie Leblanc declares a conflict of interest with Pfizer and Chugai Pharma France. Thierry Petit declares a conflict of interest with Astra-Zeneca, Novartis, Lilly, Pfizer, Roche, and MSD. The authors have no conflict of interest to declare for this specific work.

Author Contributions

Writing: Hugo Herrscher; reviewing: Julie Leblanc and Thierry Petit.

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