

Case Report

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Trastuzumab-induced thrombocytopenia after eight cycles of trastuzumab treatment

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Abstract: Trastuzumab, a humanized monoclonal antibody derived from recombinant DNA, is used in patients with breast cancer with HER2 gene amplification. The survival benefit from trastuzumab has been well established in patients with early and metastatic breast cancer who had over expression of HER2. We reported a case of severe thrombocytopenia after eight cycles of trastuzumab treatment for breast cancer. Before the 9th trastuzumab treatment, the patient's platelet decreased to $48 \times 10^9/L$. Recombinant human thrombopoietin was used, and the platelet level increased to normal level. Before the 10th treatment, the platelet count of the patient was $99 \times 10^9/L$. However, during the 10th and 11th trastuzumab treatment, the platelet count decreased to $5 \times 10^9/L$ in 24 h. After treatment with TPO and corticosteroids, the platelet levels increased to the normal level in 7 days. Trastuzumab-induced thrombocytopenia is rare but still occurred even after 8 cycles of trastuzumab treatment.

Keywords: trastuzumab, thrombocytopenia, breast cancer

1 Introduction

Drug-induced thrombocytopenia (DIT) can be evoked by a variety of medications. Although their clinical

manifestations vary, severe thrombocytopenia can develop fatal bleeding symptoms [1]. In cancer patients, it can be easily ignored by physicians because of chemotherapy-induced myelosuppression or tumor bone marrow infiltration, especially in patients with bone metastasis or adjuvant chemotherapy. DIT-related drugs have been reported to contain chemotherapeutic agents such as oxaliplatin [2], irinotecan, fludarabine [3], and monoclonal antibodies such as abciximab, infliximab, and rituximab [1], but trastuzumab-induced thrombocytopenia is very rare. This study reported a patient with life-threatening thrombocytopenia after long-term trastuzumab infusion.

2 Case report

A 35-year-old woman presented with a 3-month history of waist and back pain. Examination revealed a tumescent left supraclavicular lymph node (no mass was touched in the breast). Imaging revealed multiple hypermetabolic foci of FDG in the proximal axial bone and appendage bone as well as multiple and tumescent lymph nodes on the bilateral pulmonary hilum. There was no sign of viscera metastases. Core biopsy showed poorly differentiated metastatic breast carcinoma that was estrogen receptor positive, progesterone receptor negative, and strongly human epidermal growth factor receptor (HER2) positive (3+).

Palliative chemotherapy with docetaxel (75 mg/m^2), cisplatin (75 mg/m^2), and trastuzumab (6 mg/kg , first treatment using 8 mg/kg) was started for 6 cycles, followed by two cycles of docetaxel and trastuzumab treatment. After the treatment, CT scanning showed that all the lymph nodes disappeared and symptoms of pain all over the body had also been relieved. Nevertheless, the patient's platelet count decreased to $48 \times 10^9/L$ before the 9th treatment. Docetaxel-induced bone marrow suppression was suspected, and trastuzumab and capecitabine (1.5 g , bid, 1–14 d) were used for the 9th treatment. Meanwhile, recombinant human

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thrombopoietin (TPO) was injected to increase the platelet level. As anticipated, the platelet count returned to normal in 3 days.

Before the 10th treatment, the platelet count of the patient was $99 \times 10^9/L$ (Figure 1a). Trastuzumab and capecitabine were used again for the 10th treatment. The patient felt tiredness and nausea and all-over body petechiae, and gums bleeding occurred after a 6 h trastuzumab infusion. Blood examination showed that the platelet count was $1 \times 10^9/L$. Blood smear examination showed severe thrombocytopenia with no schistocytes, spherocytes, clumps, and giant platelets. Bone marrow biopsy showed normal megakaryocytopoiesis without signs of tumor infiltration. Heparin had never been used and other causes of thrombocytopenia such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hereditary thrombocytopenia, and hemolysis were excluded because of her normal clotting, D-dimers, immunoglobulins, hemoglobin, renal function, bilirubin, and lactate dehydrogenase as well as lack of schistocytes. After consultation with the hematologist, drug-induced thrombocytopenia was suspected. Given the treatment effect of trastuzumab, capecitabine was withdrawn and 3 weekly trastuzumab was maintained. After treatment with platelet transfusion, TPO, and corticosteroids, the platelet count returned to the normal level (Figure 1b). Trastuzumab alone was used for the 11th treatment. Dental bleeding, diffuse petechiae and ecchymosis occurred again in 24 h after the infusion and the platelet count decreased to $5 \times 10^9/L$ (Figure 1c). The new bone marrow biopsy results were consistent with the previous one. After reviewing the treatment process and referring to relevant literature, a diagnosis of trastuzumab-induced thrombocytopenia was finally made. After treatment with platelet transfusion, TPO and corticosteroids, the platelet count returned to normal.

Consent: Written consent was obtained from the patient for publication of this case report.

3 Discussion

According to the criteria proposed by George et al. to establish the relationship between a drug and thrombocytopenia [4], this patient was diagnosed with trastuzumab-induced thrombocytopenia. Cathomas et al. first reported trastuzumab-induced thrombocytopenia in a letter to the editor of *New England Journal of Medicine* in 2007 [5], while the mechanisms of trastuzumab-induced thrombocytopenia was still unclear. Drug-induced thrombocytopenia can occur as a result of direct bone marrow toxicity via impaired megakaryocyte proliferation and maturation or via immune-mediated peripheral destruction of platelets [14]. Our and previous cases all had shown a normal megakaryocytopoiesis by bone marrow biopsy [5–13]. In addition, Uppal et al. showed that trastuzumab neither directly affected platelet activation and aggregation, nor inhibited megakaryocyte differentiation [15]. Thus, trastuzumab-induced immune-mediated peripheral destruction of platelets may be the reason to thrombocytopenia.

As Table 1 showed, thrombocytopenia can occur after first exposure to trastuzumab or several cycle of trastuzumab treatment. In our article, thrombocytopenia occurred after eight cycles of trastuzumab treatment. To our knowledge, it was the longest treatment of trastuzumab before thrombocytopenia. Previous studies have suggested that thrombocytopenia caused by a first exposure to trastuzumab is related to naturally occurring antibodies that recognize the murine structural elements of trastuzumab. These antibodies bind to platelets and result in platelet clearance [8,12]. In the case of thrombocytopenia with a delayed exposure to trastuzumab, our hypothesis was that antibodies caused by first exposure to trastuzumab were insufficient. Thrombocytopenia may not occur until sufficient antibodies were produced. This speculation can also explain the relatively higher platelet nadir after the 8th treatment.

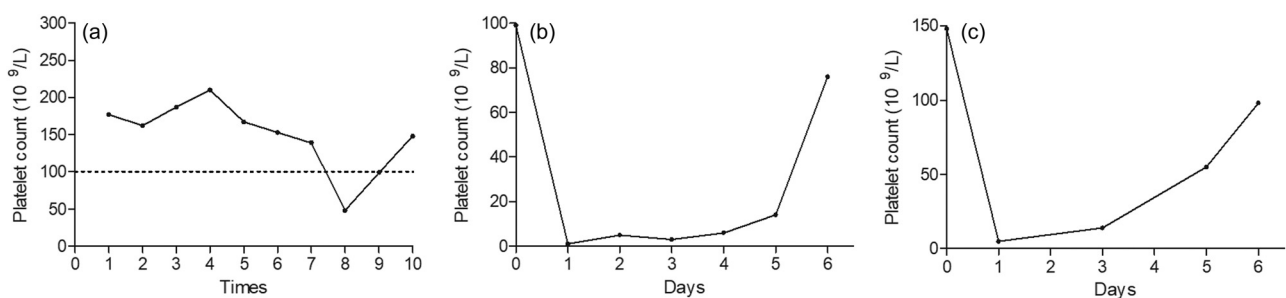


Figure 1: Platelet count changes during trastuzumab therapy: (a) before each trastuzumab infusion; (b) during the 10th infusion of trastuzumab; and (c) during the 11th infusion of trastuzumab.

Table 1: Review of patients with severe thrombocytopenia induced by trastuzumab

Cases	Age (years)	sex	HRs status	Exposure time(s) ^a	Clinical manifestation	Concurrent chemotherapy	Platelet Nadir ($\times 10^9/L$)	Management
Cathomas [5], 2007	54	F	-	1	Petechiae	No	3	IVIgs
Parikh et al. [6], 2008	56	F	+	1	Nose bleeding Tiredness nausea	No	2	Corticosteroids IVIgs
Drudi et al. [7], 2009	NM	F	NM	1	Petechial rash Echymosis	Docetaxel	7	PLT IVIgs Corticosteroids Dexamethasone PLT IVIgs
Jara Sanchez et al. [8], 2009	37	F	+	1	Petechiae	Docetaxel	3	Corticosteroids Dexamethasone Splenectomy IVIgs
Mantzourani et al. [9], 2011	56	F	-	1	Petechiae	No	5	Corticosteroids Dexamethasone Splenectomy IVIgs
Pino et al. [10], 2013	70	F	+	2	Nose bleeding Ecchymosis	Vinorelbine	2	PLT IVIgs
Aguirre et al. [11], 2013	63	F	+	NM	Petechiae	Paclitaxel	22	Corticosteroids
Zeng et al. [12], 2014	57	F	+	2	Tiredness	Abraxane Carboplatin	28	Corticosteroids Etamsylate TPO
Miarons et al. [13], 2016	70	F	-	4	None	Docetaxel	39	Corticosteroids
Present case	35	F	+	8	Petechiae Nose bleeding	Capecitabine	1	TPO PLT Corticosteroids

^a First instance of thrombocytopenia occurred after exposure to trastuzumab; F, Female; HR, Hormone receptor; IVIgs, intravenous immunoglobulin; TPO, thrombopoietin; NM, not mentioned; PLT, platelet transfusion.

Trastuzumab is an efficacy agent in breast cancer with HER2 gene amplification and can reduce 50% of risk of recurrence [16]. All but two cases discontinued trastuzumab after thrombocytopenia. One of these two cases continued because thrombocytopenia did not reappear after two cycles of trastuzumab treatments [9]. The other case continued by prolonging the interval between trastuzumab treatments, alleviating thrombocytopenia [12]. Steroids can prevent platelet removal by the reticuloendothelial system, reduce the levels of platelet-associated antibodies and increase platelet production by the bone marrow [17]. IVIG can block the Fc-receptor on macrophages of the reticuloendothelial system. This prevents phagocytosis of antibody-coated platelets and therefore inhibits platelet destruction [18]. TPO can increase platelet production by the bone marrow. Thus, these medications were used to treat drug-induced thrombocytopenia. In our case, a marked acceleration of thrombocytopenia occurred after the 10th treatment. However, the thrombocytopenia did not occur after the 9th trastuzumab treatment. The reason may be preventively using TPO. Whether preventively using TPO or other drugs such as corticosteroids and IVIG could prevent or alleviate trastuzumab-induced thrombocytopenia is worth studying.

Abbreviations

DIT	drug-induced thrombocytopenia
HER2	human epidermal growth factor receptor
TPO	recombinant human thrombopoietin
IVIG	intravenous immunoglobulin

Conflict of interest: None to declare for all the authors.

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