Severe Thrombocytopenia Induced by Second Exposure to Trastuzumab Can Be Alleviated by Prolonging the Interval Between Treatments

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Clinical Practice Points

- Trastuzumab-induced thrombocytopenia is an extremely rare, but life-threatening, condition.
- Until the present case, only 5 cases had been reported in published studies. In these cases, thrombocytopenia occurred after the first trastuzumab administration. Only 1 of the subjects had continually received trastuzumab treatment.
- In the present study, we report the case of a 57-year-old patient with breast cancer who developed severe thrombocytopenia after receiving a second dose of trastuzumab. Five days after the trastuzumab infusion, the patient was admitted to the hospital with a platelet count of 28 $\times$ 10^9/L. Thrombocytopenia recurred in the subsequent cycles.
- The patient continually received the trastuzumab treatments.
- Although the platelet count had recovered within a few days after every cycle, the patient felt tired and uncomfortable in the later stage of the treatment. Thus, we increased the interval between 2 cycles to improve her condition after the ninth cycle and achieved satisfactory results.
- Our findings have shown that trastuzumab-induced life-threatening thrombocytopenia can also occur with the second exposure to trastuzumab.
- Patients with adverse reactions to trastuzumab can still complete the trastuzumab regimen and receive satisfactory curative effects by increasing the interval between treatments.

Clinical Breast Cancer, Vol. 14, No. 2, e69-72
Keywords: Breast carcinoma, Trastuzumab, Thrombocytopenia

Introduction

Drug-induced thrombocytopenia can be caused by a number of medications. Although this condition is rare and affects only a small number of exposed patients, it is life-threatening.[1] Chemotherapeutic agents such as oxaliplatin,[2,3] fludarabine,[2] and irinotecan[4] and newly developed targeted monoclonal antibodies such as abciximab, infliximab, and rituximab,[2] have reportedly been associated with drug-induced immune thrombocytopenia. The HER-2–targeted therapeutic agent trastuzumab reportedly caused life-threatening thrombocytopenia for the first time in 2007.[5] To date, only 5 cases have been published. However, all the reports indicated that thrombocytopenia occurred at the first exposure of the patients to trastuzumab. In the present study, we report the first case of thrombocytopenia caused by a second exposure to trastuzumab. A review of the published data on this rare condition has also been provided.

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Submitted: Oct 4, 2013; Revised: Oct 28, 2013; Accepted: Nov 17, 2013; Epub: Nov 21, 2013

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Case Report

A 57-year-old woman underwent surgery with lumpectomy and axillary node dissection for localized right breast cancer on May 12, 2010. Pathologic examination revealed grade 3 invasive ductal carcinoma that was estrogen and progesterone receptor positive. In addition, the HER-2 receptor was overexpressed, and 13 of the 18 lymph nodes were positive. Adjuvant chemotherapy with 260 mg/m^2 abraxane (nanoparticle albumin-bound paclitaxel, Abraxis BioScience, Celgene, Summit, NJ), carboplatin (area under the curve = 6), and trastuzumab at a loading dose of 8 mg/kg was administered every 3 weeks starting May 26, 2010. The platelet

1526-8209/$ - see frontmatter
http://dx.doi.org/10.1016/j.clbc.2013.11.004

count was within the normal range 5, 9, 12, and 19 days after administration.

A planned second cycle of trastuzumab at a reduced dose (6 mg/kg) was administered 21 days after the first administration. After 5 days, the patient felt tiredness but showed no signs of spontaneous bleeding. Investigation revealed a platelet count of 28 $\times$ 10^9/L, and the hemoglobin and white blood cell counts were within the normal range. The patient was examined by a hematology team, and oral etamsylate was recommended to prevent spontaneous bleeding. The platelet count recovered during the next 7 days and remained within the normal range before the third cycle.

A modified third cycle (carboplatin, area under the curve = 4) was then administered. After 4 days, the platelet count had decreased to 19 $\times$ 10^9/L, but the patient showed no signs of spontaneous bleeding. The patient received oral etamsylate and an injection of 15,000 U of recombinant human thrombopoietin (3SBio, Shenyang, China) for 3 days. Her platelet count had fully recovered within the next 9 days. In the fourth cycle, the dose and schedule of the regimen was adjusted further. The abraxane dose was reduced to 180 mg/m^2, and trastuzumab was administered 1 day before the chemotherapeutic agents were given. A recombinant human thrombopoietin injection was given to the patient 24 hours after chemotherapy. At 4 days after chemotherapy, the platelet count was 39 $\times$ 10^9/L. A bone marrow biopsy showed normal megakaryocytopoiesis without signs of tumor infiltration. The platelet count had fully recovered during next 8 days without any intervention.

A planned fifth cycle was administered. The patient complained of severe tiredness and dental bleeding 24 hours after a single infusion of trastuzumab. Consequently, the abraxane and carboplatin infusion was delayed, and a full blood count was conducted. The platelet count was 20 $\times$ 10^9/L. Oral etamsylate was then given to the patient. A platelet transfusion was recommended, but the patient refused. Although the platelet count had fully recovered during the next 8 days, the patient remained in poor condition. After a multidisciplinary discussion, the chemotherapy was stopped, and the patient underwent radiotherapy. Afterward, the remaining 2 cycles of adjuvant chemotherapy were administered at 3-week intervals. No adverse event occurred during the radiotherapy and adjuvant chemotherapy.

Trastuzumab treatment at a loading dose of 6 mg/kg was restarted on December 30, 2010 and administered every 3 weeks. No adverse event occurred. A planned seventh cycle was administered 21 days after the sixth cycle. Three days after treatment, the laboratory test results revealed a platelet count of 60 $\times$ 10^9/L. Without any special intervention, the platelet count had reached normal levels within 8 days. Although the laboratory test results showed no abnormal findings, the patient felt tired and was in poor physical condition. Thus, we decided to increase the interval between the 2 trastuzumab therapy cycles from 21 days to 40 days to improve her physical condition in the ninth cycle. The result was satisfactory. Finally, we gradually reduced the interval from 40 days to 30 days by monitoring her physical condition within 6 cycles. During the last 3 cycles, we observed significantly shorter recovery times for the platelet count compared with those required during the early cycles (2.33 vs. 7.15 days). A follow-up examination was

Table 1 Clinical Data of Patients With Severe Thrombocytopenia Induced by Trastuzumab

Source	Age (Years)	Gender	Cycle TB Observed	Symptoms[a]	Platelet Nadir ($\times$ 10^9/L)	Single-agent Used	Continuous Trastuzumab Therapy	Day TB Observed[b]	Treatment	Interval to Reach Normal (Day)[c]
Present case	57	F	Second	Tiredness	28	No	Yes	5	None	7
Cathomas et al,[5] 2007	54	F	First	Nosebleed, petechiae	3.0	No	No	4	IVIG	7
Parikh et al,[8] 2008	56	F	First	Petechial rash	2.0	Yes	No	10 hours	IVIG	5
Jara Sanchez et al,[11] 2009	37	F	First	Petechiae	3.0	No	No	1	Platelet transfusion, dexamethasone infusion, and IVIG	4
Drudi et al,[10] 2010	NR	F	First	Cutaneous hemorrhage	7.0	No	No	19	Platelet transfusion, IVIG	NR
Mantzourani et al,[9] 2011	56	F	First	Petechiae, nose bleed	5.0	No	Yes	3	IVIG	5

Abbreviations: F = female; IVIG = intravenous immunoglobulin; NR = not reported; TB = thrombocytopenia.
[a]The described symptom was at the first occurrence of TB.
[b]From the beginning of trastuzumab administration.
[c]From the presence of TB.