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Trastuzumab Induced Thrombocytopenia: A Case Series

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ABSTRACT

Background: Trastuzumab is a cornerstone of treatment for HER2-positive malignancies and is generally well tolerated. While cardiotoxicity and infusion-related reactions are recognized adverse effects, trastuzumab-induced thrombocytopenia remains a rare complication, with fewer than 25 cases reported in the literature. We present a series of six patients with HER2-positive breast cancer who developed thrombocytopenia temporally associated with trastuzumab therapy.

Methods: A retrospective review was conducted at a tertiary cancer center to identify patients who developed thrombocytopenia during trastuzumab therapy between 2020 and 2025. Histopathologically confirmed HER2-positive breast cancer patients receiving trastuzumab were included. All patients underwent evaluation for alternative causes of thrombocytopenia, including peripheral smear examination, coagulation studies, viral markers, and bone marrow assessment. Drug causality was assessed using the Naranjo Adverse Drug Reaction Probability Scale.

Results: Six patients were identified. Median age was 46 years (range, 39–52 years). Thrombocytopenia developed after a median of 3.5 trastuzumab cycles (range, 2–7 cycles), with onset occurring 1–3 weeks following exposure. Median nadir platelet count was 51 × 10^9/L (range, 30–63 × 10^9/L). Four patients (66.7%) developed CTCAE grade 2 thrombocytopenia and two (33.3%) developed grade 3 thrombocytopenia. Naranjo scores ranged from 5 to 8, supporting probable drug causality. All patients received corticosteroids, two additionally received thrombopoietin receptor agonists, and one required platelet transfusion. Platelet recovery was observed in all patients, with a median recovery time of 10 days (range, 5–20 days). All 6 patients experienced recurrent episodes following subsequent trastuzumab exposures, however, four patients successfully completed all 17 planned trastuzumab cycles with appropriate supportive management.

Conclusions: Trastuzumab-induced thrombocytopenia is an uncommon but clinically significant adverse event that may occur after multiple uneventful treatment cycles and can recur with subsequent exposures. Unlike most published reports describing profound thrombocytopenia shortly after initial trastuzumab administration, our series demonstrates a milder but recurrent pattern of toxicity. Early recognition, exclusion of alternative etiologies, and individualized supportive

management may permit continuation of trastuzumab therapy in selected patients.

Keywords: Trastuzumab, HER2-positive breast cancer, Breast cancer, Thrombocytopenia, Case report, Platelet transfusion, Chemotherapy, Drug-induced thrombocytopenia, Targeted therapy, Radiation therapy

INTRODUCTION

Trastuzumab, a monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2), has become a standard of care for the treatment of HER2-positive cancers. While generally used as systemic therapy for HER2-positive breast cancers, several studies have demonstrated the clinical benefit of adding Trastuzumab to chemotherapy regimens in metastatic disease as well as treatment of HER2-positive gastric cancers.[1] However, as with any therapeutic agent, Trastuzumab is not without its side effects.

Although well tolerated, Trastuzumab is known to cause cardiotoxicity, especially when used with anthracycline based chemotherapy regimens. In some studies, the incidence of cardiotoxicity including congestive heart failure and decrease in left ventricular ejection fraction has been reported as high as 44%.[2] Some infusion reactions also include angioedema, anaphylaxis, interstitial pneumonitis, and acute respiratory distress syndrome. However, thrombocytopenia is a rare adverse effect of Trastuzumab therapy, with less than 25 cases documented in the English literature, summarised in Table 1.

Here we present six cases of breast cancer who developed thrombocytopenia after Trastuzumab.

METHODS

A retrospective review of medical records was performed to identify patients that developed thrombocytopenia during trastuzumab therapy from the year 2020 to 2025 at our institute. Histopathologically confirmed HER2 positive cases of invasive breast carcinoma that underwent trastuzumab therapy were included. A total of 6 cases were identified and data were extracted.

During treatment, all cases had undergone a complete thrombocytopenia workup including complete blood count, peripheral smear, reticulocyte count, coagulation profile, viral markers, and bone marrow biopsy, all of which were unrevealing. No alternative etiology was identified for any of the cases.

A formal drug causality assessment was done retrospectively with the Naranjo Adverse Drug Reaction Probability Scale for each of the cases.

RESULTS

A total of six patients with HER2-positive breast cancer were identified as having trastuzumab-induced thrombocytopenia during the study period (Table 1). The median age at presentation was 46 years (range, 39-52 years). Clinical stage at diagnosis ranged from cT2N0M0 to cT4bN2aM0, with most patients presenting with locally advanced disease.

Thrombocytopenia developed after a median of 3.5 cycles of trastuzumab (range, 2-7 cycles). The onset of thrombocytopenia occurred between 1 and 3 weeks following trastuzumab administration, with four patients (66.7%) developing thrombocytopenia within one week of exposure. The nadir platelet count ranged from 30×10^9/L to 63×10^9/L, with a median nadir platelet count of 51×10^9/L. Four patients (66.7%) developed grade 2 thrombocytopenia, whereas two patients (33.3%) developed grade 3 thrombocytopenia as per CTCAE.

All patients underwent evaluation to exclude alternative causes of thrombocytopenia including peripheral smear, reticulocyte count, coagulation profile, viral markers, and bone marrow biopsy, all of which were unrevealing. Naranjo adverse drug reaction probability scores ranged from 5 to 8, corresponding to probable causality. Based on the temporal association with trastuzumab

administration, exclusion of competing etiologies, and drug causality assessment, a diagnosis of trastuzumab-induced thrombocytopenia was established in all cases.

Corticosteroids were administered in all six patients. Patient 2 received prednisone 5mg twice a day for 5 days, while patients received dexamethasone 4mg twice a day for 5 days. Two patients additionally received thrombopoietin receptor agonists, while one patient required platelet transfusion because of the severity of thrombocytopenia. Platelet recovery was observed in all patients, with a median recovery time of 10 days (range, 5-20 days).

Table 1: Summary of breast cancer cases identified with trastuzumab induced thrombocytopenia.

Age (years)	Stag	Incidence after number of cycles	Time after Trastuzumab exposure	Nadir Platelet Count (10^9/L)	Management	Time before recovery	Naranjo Score
39	cT4bN1M0	2	3 weeks	56	Steroids, Platelet transfusion	1 week	6
45	cT2N0M0	3	25 days	30	Steroids	1 week	8
47	cT4bN2aM0	7	2 weeks	35	Steroids, TPO-RA	2 weeks	5
52	cT3N1M0	4	1 week	50	Steroids	5 days	6
44	cT4aN0M0	6	1 week	52	Steroids, TPO-RA	13 days	6
52	cT3N1M0	2	1 week	63	Steroids	20 days	5

Patient 1

A 39-year-old premenopausal female with left breast carcinoma, cT4bN1M0, ER/PR-positive and HER2-positive, received neoadjuvant TCH (Trastuzumab, Carboplatin and Trastuzumab) chemotherapy. She developed thrombocytopenia after the second cycle of TCH, with a nadir platelet count of 56,000/µL, which improved following dexamethasone and supportive care, allowing continuation of treatment (Fig 1). A second episode occurred after the fifth cycle of TCH, with platelet counts declining to 75,000/µL, again recovering with conservative management. Following completion of six cycles of TCH, she underwent modified radical mastectomy with pathological complete response (ypT0N0) and subsequently received adjuvant radiotherapy and trastuzumab maintenance. Recurrent thrombocytopenia persisted during adjuvant trastuzumab, with platelet counts declining to 72,000/µL after the seventh cycle resulting in temporary treatment delays and one episode requiring platelet transfusion. After recovery, trastuzumab was successfully rechallenged and continued. The patient ultimately completed all 17 planned cycles of trastuzumab and remains on adjuvant endocrine therapy with ongoing follow-up.

Patient 2

A 45-year-old postmenopausal female with right breast invasive ductal carcinoma, cT2N0M0, ER/PR-positive and HER2-positive, underwent breast-conserving surgery followed by adjuvant treatment consisting of four cycles of AC (Adriamycin and Cyclophosphamide), weekly paclitaxel with trastuzumab (TH), adjuvant radiotherapy, maintenance trastuzumab, and endocrine therapy with letrozole. Platelet counts remained within the normal range during AC chemotherapy but declined progressively during TH, with thrombocytopenia first becoming clinically significant after the third TH cycle, when the platelet count decreased to 41,000/µL. Following recovery with conservative management, treatment was resumed. During adjuvant trastuzumab, recurrent episodes of thrombocytopenia were

observed, with platelet counts falling to 60,000/µL, 30,000/µL (nadir), 72,000/µL, 58,000/µL, 52,000/µL, and 86,000/µL on serial follow-up assessments. The patient remained free of major bleeding manifestations and was managed with repeated courses of oral prednisolone, temporary treatment interruptions, and hematology consultation. Despite multiple recurrences, trastuzumab was successfully rechallenged after platelet recovery on each occasion, allowing completion of all 17 planned trastuzumab cycles. She remains on adjuvant letrozole and has been under follow-up without further reported complications.

Patient 3

A 47-year-old female with carcinoma left breast cT4bN2aM0 (ER/PR-negative, HER2-positive), received neoadjuvant HER2-directed chemotherapy comprising one cycle of trastuzumab-docetaxel followed by three cycles of TCH, after which she underwent a left skin-sparing mastectomy on 11 December 2023. Following surgery, she received one additional cycle of TCH, adjuvant radiotherapy to the chest wall and regional lymphatics. During maintenance trastuzumab, she developed recurrent episodes of thrombocytopenia, first detected after the seventh cycle with a platelet count of 97,000/µL, followed by further episodes after the eighth cycle (93,000/µL), twelfth cycle (100,000/µL), thirteenth cycle (73,000/µL), fourteenth cycle (86,000/µL), fifteenth cycle (35,000/µL; nadir), and sixteenth cycle (89,000/µL). In each instance, trastuzumab administration was deferred until platelet recovery along with administration of corticosteroids and thrombopoietin receptor agonist (TPO-RA) , following which treatment was successfully resumed, allowing completion of all 17 planned trastuzumab cycles. The patient however later developed metastatic recurrence in January 2025 with a biopsy proven metastatic liver disease, for which she received systemic therapies including lapatinib and capecitabine. However, no further episodes of thrombocytopenia were documented, supporting a likelihood of trastuzumab related etiology. The patient subsequently experienced progression of metastatic disease best supportive care.

Patient 4

A 52-year-old female with HER2 enriched carcinoma left breast cT3N1M0 received neoadjuvant chemotherapy comprising four cycles of AC followed by four cycles of TH. The first episode of thrombocytopenia was documented after the fourth cycle of TH on 11 August 2023, with a platelet count of 66,000/µL. Following recovery with corticosteroid therapy, she underwent modified radical mastectomy and adjuvant radiotherapy. Maintenance trastuzumab was continued. However, recurrent thrombocytopenia was observed after subsequent trastuzumab exposures, with platelet counts declining to 74,000/µL after the sixth cycle, 82,000/µL after the seventh cycle, 71,000/µL after the ninth cycle, and reaching a nadir of 50,000/µL after the tenth cycle. Each episode occurred following trastuzumab administration and improved after treatment interruption and steroid therapy. Due to repeated episodes of thrombocytopenia, trastuzumab was permanently discontinued after the tenth cycle. The patient remains on follow-up with no further documented episodes of thrombocytopenia.

Patient 5

A 44-year-old female with carcinoma right breast, cT4aN0M0, received neoadjuvant chemotherapy comprising four cycles of AC followed by four cycles of TH, after which she underwent definitive surgery on 8 November 2024 and subsequently received adjuvant radiotherapy. Maintenance trastuzumab was initiated thereafter. The first episode of thrombocytopenia was documented following the sixth trastuzumab cycle, with a platelet count of 52,000/µL recorded on 24 January 2025. Despite recovery with corticosteroids and TPO-RA therapy, recurrent episodes of

thrombocytopenia were observed following subsequent trastuzumab exposures, with platelet counts declining to 63,000/µL after the eighth cycle, 68,000/µL after the ninth cycle, 58,000/µL after the twelfth cycle, 72,000/µL after the fifteenth cycle, and 83,000/µL after the sixteenth cycle. In each instance, platelet counts improved with treatment interruption and supportive therapy, permitting successful rechallenge. Despite multiple recurrent episodes demonstrating a clear temporal relationship with trastuzumab administration, the patient completed all 17 planned cycles of trastuzumab and remains on follow-up without persistent thrombocytopenia.

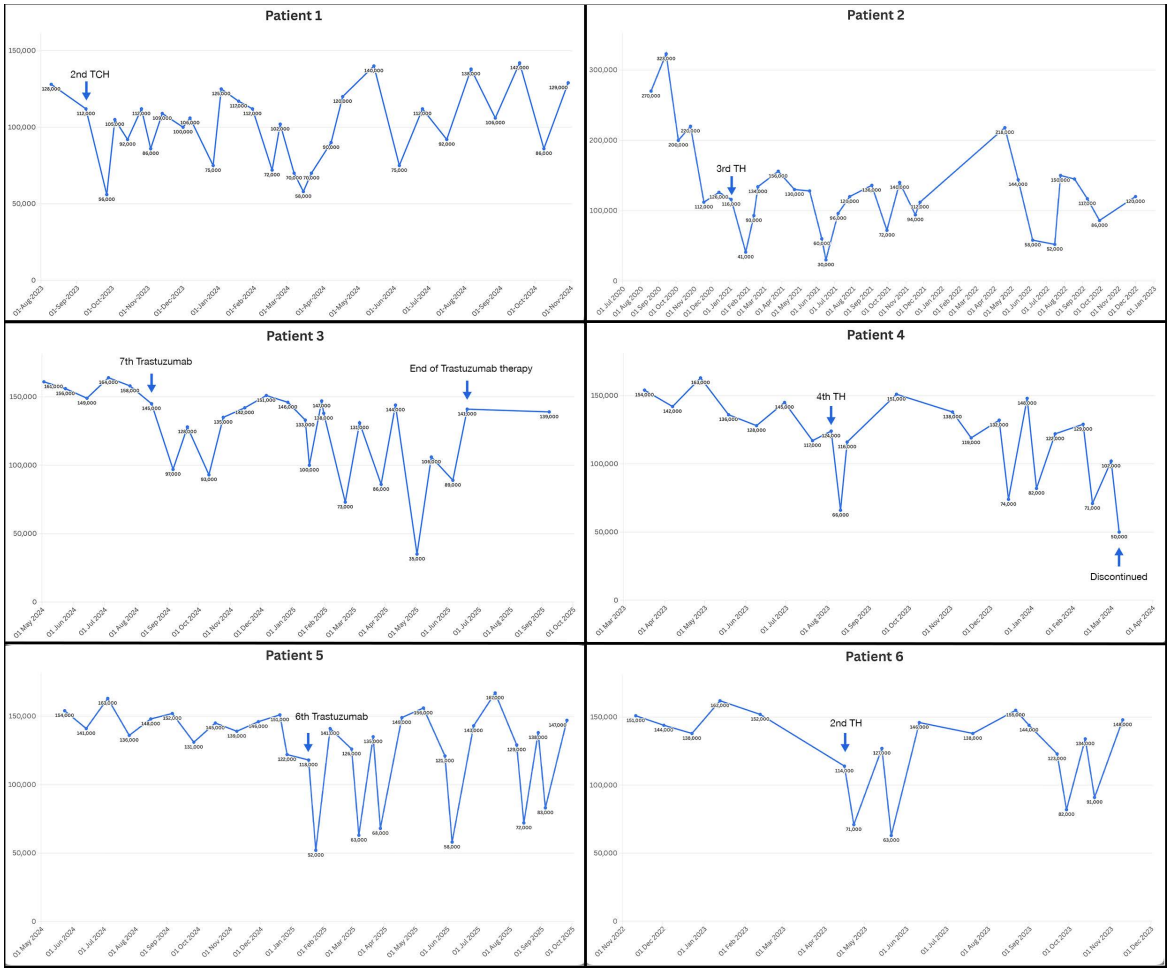

Figure 1: Platelet change trend of patients 1-6 during trastuzumab therapy.

Patient 6

A 52-year-old female with carcinoma right breast, cT3N1M0, received neoadjuvant chemotherapy consisting of four cycles of AC, followed by 1 cycle of TH. The first episode of thrombocytopenia occurred early during treatment after the second TH cycle, when the platelet count decreased to 71,000/µL on 23 April 2023. Following recovery with corticosteroid therapy, treatment was continued. However, a second episode developed after the third TH cycle, with a further decline in platelet count to 63,000/µL after fourth TH. The patient subsequently underwent surgery on 21 July 2023 followed by adjuvant radiotherapy, after which maintenance trastuzumab was started. Recurrent thrombocytopenia was again observed following the sixth trastuzumab cycle (platelet count 82,000/µL) and the seventh trastuzumab cycle (platelet count 91,000/µL). Each episode improved with corticosteroid therapy and temporary treatment interruption, allowing subsequent trastuzumab administration. The patient continued treatment through the eighth

maintenance trastuzumab cycle but was subsequently lost to follow-up.

DISCUSSION

While trastuzumab is generally well-tolerated, thrombocytopenia is a rare and unusual adverse event associated with its use, with only a limited number of cases documented in the literature (Table 2). Trastuzumab-induced thrombocytopenia appears to be primarily immune-mediated.[3,4] In a case with strong laboratory correlation, Sullivan et al. detected drug-dependent platelet antibodies that bound platelets in the presence of trastuzumab, supporting an immune mechanism of accelerated platelet clearance.[22] Chen et al. further demonstrated trastuzumab- and complement-mediated platelet destruction in vitro, with patient platelets enriched for HER2 undergoing rapid lysis when exposed to trastuzumab and complement, suggesting a trastuzumab–HER2–complement pathway as a plausible mechanism for acute, severe thrombocytopenia. [25] Together, these findings indicate that trastuzumab can trigger immune-mediated platelet destruction via drug-dependent antibodies and complement activation, rather than through direct suppression of platelet production. [7,22,25]

The cases presented here illustrate the recurrent and persistent nature of this rare complication, requiring steroids, conservative management with treatment gaps, and even platelet transfusion. The patients developed thrombocytopenia after every cycle of trastuzumab, with platelet counts recovering during treatment gaps. Thrombocytopenia persisted even after switching to trastuzumab monotherapy, ruling out the involvement of other anti-cancer agents.

The clinical characteristics of our patients were broadly consistent with previously published reports of trastuzumab-induced thrombocytopenia, while also demonstrating a comparatively milder clinical spectrum. Most published cases describe severe thrombocytopenia occurring after the first or second exposure to trastuzumab, often within hours to a few days of administration, with nadir platelet counts frequently below 10 × 10^9/L and requiring intensive interventions such as platelet transfusions, intravenous immunoglobulin (IVIG), corticosteroids, and occasionally plasmapheresis. In contrast, thrombocytopenia in our series developed after 2–7 cycles of trastuzumab, with onset occurring 1–3 weeks following exposure and nadir platelet counts ranging from 30–63 × 10^9/L. None of our patients developed profound thrombocytopenia comparable to that reported by Pino et al., Sullivan et al., Wang et al., Takano et al., or Chen et al., where platelet counts fell to ≤3 × 10^9/L. [9,11,22,24,25]

These cases highlight the challenging situation clinicians face when an essential therapy like trastuzumab becomes self-limiting due to a rare but significant adverse effect.[5] The development of thrombocytopenia necessitated multiple treatment gaps, which could potentially impact the efficacy of trastuzumab and the overall treatment outcome. The delayed onset after multiple trastuzumab cycles observed in several of our patients supports the growing recognition that trastuzumab-induced thrombocytopenia is not exclusively an early-cycle phenomenon and may occur even after repeated uneventful exposures, emphasizing the need for continued vigilance throughout the course of HER2-directed therapy.

For patients with features of idiopathic thrombocytic purpura, treatment with high-dose dexamethasone has shown to be highly beneficial, and successfully used for the management of trastuzumab induced thrombocytopenia. [6,7] A 3-weekly schedule of Romiplostim can also be considered alongside Trastuzumab therapy as suggested by Rainone et al., 2023 in their series of 6 cases.[8]

The risk-benefit analysis of continuing trastuzumab therapy in the face of persistent thrombocytopenia is complex. On one hand, the potential risk of bleeding complications due to severe thrombocytopenia must be weighed against the well-established benefits

of trastuzumab in improving outcomes for HER2-positive cancer patients. On the other hand, alternative treatment options should be explored.

Cathomas and von Moos reported that lapatinib seemed to be safely used in patients who had experienced severe thrombocytopenia with trastuzumab in second-line treatment.[9] Though the efficacy is not superior to Trastuzumab therapy.[10] An alternate regime of weekly trastuzumab at a lower dose was attempted post thrombocytopenia by Wang et al., but the patient still developed recurrent thrombocytopenia. [11]

In terms of future research directions, investigating predictive biomarkers or risk factors for trastuzumab-induced thrombocytopenia could aid in identifying high-risk patients and guiding personalized treatment decisions. Additionally, exploring the underlying mechanisms, potentially through preclinical models, may uncover preventive strategies or alternative targeted therapies with a lower risk of thrombocytopenia.[12]

CONCLUSION

While trastuzumab-induced thrombocytopenia is a rare occurrence, our case series highlights the need for vigilant monitoring and judicious management when faced with this adverse event. A multidisciplinary approach may be warranted to navigate the complexities of balancing the risks and benefits of continuing trastuzumab therapy while ensuring patient safety and optimal treatment outcomes. Further clinical trials for establishment of risk factors for trastuzumab induced thrombocytopenia may be warranted.

Table 2: Cases of trastuzumab induced thrombocytopenia reported in literature

Author, Year	Age	Diagnosis	Incidence after number of cycles	Time after Trastuzumab exposure	Nadir Platelet Count (10^9/L)	Management	Time before recovery
Cathomas et al., 2007 [13]	54	Breast Cancer	1	4 days	3	IVIG	7 days
Parikh et al., 2008 [14]	56	Breast Cancer	1	10 hours	2	IVIG	5 days
Jara Sánchez et al., 2009 [7]	37	Breast Cancer	1	1 day	3	Platelet transfusion, Steroids, IVIG	4 days
Drudi et al., 2010 [5]	N/A	Breast Cancer	1	19 days	7	Platelet transfusion, Steroids, IVIG	N/A
Mantzourani et al., 2011 [15]	56	Breast Cancer	1	3 days	5	IVIG	5 days
Aguirre et al., 2013 [16]	63	Breast Cancer	6 months (weekly)	N/A	22	Steroids	7 days
Pino et al., 2013 [17]	70	Breast Cancer	1*	24 hours	0	Platelet transfusion, Steroids, IVIG	7 days
Zeng et al., 2014 [18]	57	Breast Cancer	2	5 days	28	Oral Etamsylate	7 days
Miarons et al., 2016 [19]	70	Breast Cancer	4	N/A	39	Steroids	N/A
Luo et al., 2019 [20]	39	Breast Cancer	5	10 days	3	Platelet transfusion, recombinant human GCSF, recombinant	4 days

						human IL, etamsylate	
Zhou et al., 2020 [21]	35	Breast Cancer	8	N/A	48	TPO-RA	3 days
Sullivan et al., 2020 [22]	48	Salivary Duct Cancer	1	5 days	1	Platelet transfusion, Steroids, IVIG, Plasmapheresis	2 days
Zeng et al., 2020 [23]	29	Breast Cancer	2	6 hours	3	Platelet transfusion, steroids, oxytocin	11 days
Wang et al., 2021 [11]	52	Breast Cancer	1	5 days	1	Platelet transfusion, Steroids	6 days
Takano et al., 2022 [24]	57	Gastric Cancer	1	8 days	1	Platelet transfusion, Steroids	6 days
Chen et al., 2022 [25]	51	Breast Cancer	1	6 hours	2	Platelet transfusion, IVIG, TPO-RA	6 days
Kucera et al., 2023 [26]	70s	Endometrial Cancer	1	1 week	0	Platelet transfusion, Steroids, IVIG	N/A
Rainone et al., 2023 [8]	57	Breast Cancer	1	N/A	52	TPO-RA	N/A
Rainone et al., 2023 [8]	53	Breast Cancer	1	N/A	91	TPO-RA	N/A
Rainone et al., 2023 [8]	36	Breast Cancer	1	N/A	24	TPO-RA	N/A
Rainone et al., 2023 [8]	57	Breast Cancer	1	N/A	50	TPO-RA	N/A
Rainone et al., 2023 [8]	58	Breast Cancer	1	N/A	57	TPO-RA	N/A
Rainone et al., 2023 [8]	80	Breast Cancer	1	N/A	50	TPO-RA	N/A

IVIG = Intravenous Immunoglobulin, TPO-RA = Thrombopoietin Receptor Agonists, GCSF = Gram Colony Stimulating Factor, IL = Interleukin, N/A = Not Available
*1st cycle of 2nd line therapy with trastuzumab, after uneventful completion of 1 year of trastuzumab therapy

Declaration by Authors

Ethical Approval: Approved by the Institutional Ethics Committee of Vardhman Mahavir Medical College & Safdarjung Hospital

Patient Consent: Written, informed consent was obtained from all patients for the use of their clinical details for the purpose of publication.

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