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Case Report

Trastuzumab Induced Thrombocytopenia in Early Breast Cancer: Case Report and Review of Literature

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Abstract

Thrombocytopenia is a commonly encountered during course of chemotherapy. Breast cancer is the most common cancer in women worldwide. A 58 years old lady, diagnosed case of carcinoma breast left side (early stage) on adjuvant trastuzumab therapy developed progressive thrombocytopenia. The treatment was stopped and started on oral steroids. The platelet count recovered slowly on oral steroids. In this review we have highlighted a very rarely encountered side effect of trastuzumab induced thrombocytopenia.

Keywords: Trastuzumab; Breast Cancer; Thrombocytopenia; Her 2 neu

Introduction

Thrombocytopenia is a commonly encountered during course of chemotherapy. Drug-induced immune thrombocytopenia is seen with several chemotherapeutic agents like oxaliplatin, irinotecan and fludarabine [1-3]. It is also seen in newer targeted monoclonal antibodies like rituximab, abciximab and infliximab [4]. Breast cancer is the most common cancer in women worldwide. The prognosis and outcome is based on multiple factors including hormone receptor status and Her 2 neu positivity. Discovery of the molecularly targeted therapy, trastuzumab has given a new ray of hope for Her 2 neu positive patients trastuzumab is usually well tolerated. Thrombocytopenia a very rare complication and we report here the tenth reported case of trastuzumab induced thrombocytopenia. As trastuzumab is an important adjuvant treatment in case of Her 2 neu positive early breast cancer patients, development of thrombocytopenia remains a challenge towards completion of therapy.

Case Presentation

A 58 years old post-menopausal patient diagnosed as carcinoma breast left side (early stage) underwent left breast conservation surgery with axillary lymph node dissection. The post-operative histopathology was infiltrating ductal carcinoma grade III, p (T2 N0M0) oestrogen/progesterone (ER/PR) negative and Her 2 neu positive. The patient received adjuvant external beam radiotherapy to left breast and boost to lumpectomy cavity to a dose of 62Gy/32fractions. Two weeks following the completion of radiotherapy, the patient received 6 cycles of adjuvant chemotherapy 5-flurouracil 500mg/m^2+ epirubicin 100mg/m^2 + cyclophosphamide 500mg/m^2 (FEC) three weekly regimen, the complete blood count (CBC) was normal throughout course of chemotherapy. Patient tolerated chemotherapy well without any treatment interruptions. Three weeks after completion of chemotherapy, targeted monoclonal antibody therapy trastuzumab was started. The blood investigations and 2D-ECHO was normal. First cycle of Trastuzumab was started at a loading dose 8mg/kg and subsequently maintenance dose of at 6mg/kg was given as per the three weekly trastuzumab regimen. The patient's platelet counts dropped gradually as indicated in the Table 1. At the start of fourth cycle, the platelet count was 91,000/mm^3 but the treatment was continued. At the beginning of the seventh cycle, the count dropped to 52,000/mm^3. The treatment was deferred and platelet counts repeated a week later, showed a platelet count of 42,000/mm^3. The patient was thoroughly investigated; she had no recent onset of fever or any other illness in the recent past. There was no hepato-splenomegaly. Work up for Malaria and IgG, IgM dengue tests were done as it is an endemic disease in this part of the world. She was also tested for retroviral positivity and was negative. The peripheral smear was showing normocytic normochromic anaemia with thrombocytopenia without megakaryocytosis or smudge cells. Due to persistent thrombocytopenia suspecting immune thrombocytopenia (ITP) bone marrow aspiration and biopsy were done. The patient was started on short course of steroid, oral prednisolone at 1mg/kg for period of 2 weeks and was tapered over next 1 week, after which the platelet counts improved. Meanwhile the bone marrow report showed normocytic normochromic picture with thrombocytopenia, there was no involvement of bone marrow. On stopping the short course steroids, the counts reduced further. Hence autoimmune thrombocytopenia (trastuzumab induced) was considered as the diagnosis of exclusion. The patient was restarted on oral prednisolone 1mg/kg with dose and continued on tapering doses upto 5 months. The platelet counts recovered over the period of as indicated in the Table 1. During the course of the steroids, the patient developed pneumonia and steroids induced hyperglycemia which was managed accordingly. It was decided not continue with trastuzumab after the recovery of counts. Two years after the stopping of trastuzumab, the patient is disease free. She received a total 6 cycles of trastuzumab.

Discussion

Trastuzumab is humanized monoclonal antibody acting on trans-membrane protein complex her2 neu/ERBB. It is used both in the adjuvant and metastatic setting and has shown good disease free interval in breast cancer. The most frequently encountered complication of trastuzumab in the clinical practice is the reversible cardiac failure. Myelosuppression is a rarely expected complication of trastuzumab therapy. Thrombocytopenia during trastuzumab

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Table 1: Platelet Count during the Course of Treatment.

	Week	Platelet Count (lakh/cumm)
Start of Chemotherapy	0	1.56
	3	1.72
	6	1.49
	9	1.92
	12	2.14
	15	1.72
Start of Trastuzumab	20	1.76
	23	1.16
	26	1.64
	29	0.91
	32	0.7
	35	0.52
	36	0.42
Start of Short Steroid Therapy	38	0.49
	40	1.48
Stop Steroid	41	1.46
Restart Steroid	43	0.62
	45	0.81
	47	0.94
	49	1.12
	52	1.52
	55	1.66
	58	1.66
	61	1.72
	64	1.94
	67	2.24
	70	2.12
	73	2.1
	76	2.23
	79	2.05
	82	2.11

therapy is very rare, trials have shown grade III thrombocytopenia in about 13% of cases with ado-trastuzumab, more so because it contains cytotoxic drug in an antibody-drug conjugation [5]. So far only 9 cases have been reported with thrombocytopenia attributable to trastuzumab use.

Drug induced thrombocytopenia can be classified into one of the following mechanism, fiban-induced thrombocytopenia, hapten-dependent antibody, drug-specific antibody, immune complex, drug-dependent antibody, autoantibody induction (Table 2). However monoclonal antibody induced thrombocytopenia, in addition to the above mechanisms can also be due to decreased haematopoiesis, infusion reactions due to cytokine release and type III hypersensitive reactions, haemophagocytosis, thrombotic microangiopathy, bone marrow suppression and very rarely bone marrow involvement of tumour cells. Drug induced thrombocytopenia is a diagnosis by

Table 2: Classification of the Mechanisms of Drug Induced Thrombocytopenia.

S. No	Mechanisms of Drug Induced Thrombocytopenia	Examples
1	Fiban-induced thrombocytopenia	Epitifibatide
2	Hapten-dependent antibody	Penicillin,
3	Drug-specific antibody	Abciximab
4	Immune complex	Heparin
5	Drug-dependent antibody	Non-steroidal anti-inflammatory drugs
6	Autoantibody induction	Procainamide

exclusion. This is well established by the notable work of George. JN et al., wherein he has proposed criteria for drug induced thrombocytopenia [6]. There are four criteria, they are as follows:

1) Therapy with the candidate drug preceded thrombocytopenia.

2a) Recovery from thrombocytopenia was complete and sustained after therapy with the drug was discontinued.

2b) The candidate drug was the only drug used before the onset of thrombocytopenia or other drugs were continued or re-introduced after discontinuation of therapy with the candidate drug with a sustained normal platelet count.

3) Other causes for thrombocytopenia were excluded.

4) Re-exposure to the candidate drug resulted in recurrent thrombocytopenia.

All four criteria is definitive of drug induced thrombocytopenia. Atleast criteria number 1 is required to consider drug induced thrombocytopenia.

This review is presented after the survey of the literature available of trastuzumab induced thrombocytopenia. A total of 9 cases have been reported so far. We have added our case to the available literature. The detailed summary of the cases including our case presented as in Table 2. From the limited literature available the age of the patients in all the cases so far except one is above the age of 50 years, all cases are early breast cancer (EABC) except one which is a metastatic disease. All the cases received trastuzumab as first line therapy except one case; it was given subsequent line of treatment after 1st line therapy. Thrombocytopenia was noted in the first cycle itself except two cases wherein it was noted in the second cycle in one case and progressive thrombocytopenia in the other case. The most common presenting symptoms is the bleeding manifestations like nose bleed, petechiae, life threatening bleeding manifestations and tiredness in one case and asymptomatic in another case. The interval between presenting symptom and the exposure to trastuzumab is in the range of 10 hours to 19 days, whereas in two cases there was a constant decline with every cycle administered. The platelet counts have been in the range of 2000/mm^3 to 39000/mm^3. Treatment given in all these cases has been methylprednisolone infusion, IVIg infusion, oral prednisolone and platelet transfusion. The time for platelet recovery is in the range 5 to 13 days, in one case the there was continuous use of oral steroids for recovery of the platelet count.

With respect to the report, the patient is an elderly lady with early breast cancer, ER/PR negative and Her2neu positive status, treated with breast conservative therapy. Our case report is almost similar

to Marions et al. [15] in our case as there was no other agent used, other than trastuzumab. As bone marrow studies excluded ITP and bone marrow involvement, final diagnosis was made as autoimmune thrombocytopenia due to trastuzumab, because the platelet count recovered with oral steroid therapy.

Conclusion

From this review we can infer that trastuzumab induced thrombocytopenia is usually acute, mostly seen after first cycle of trastuzumab and can be life threatening with bleeding manifestations, however gradual onsent thrombocytopenia can also be a presentation as seen in the recent case reports. A through work up needs to be done in case of progressive thrombocytopenia. The age of presentation is also seen in patients above 50 years of age. This is an important causal observation, the exact reason has to ascertained. The most probable cause could be because of the bone marrow suppression with prior chemotherapy, which takes a long time to recover. Also the polypharmacy (use of multiple other drugs) can cause drug-drug interaction in elderly patients. Except one case report, all have had thrombocytopenia in early breast cancer and when used as first line adjuvant treatment. Whenever present in a curative setting like the 9 cases including ours it becomes a therapeutic challenge.

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