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Imatinib Related Severe Anaemia In a Case of Chronic Myeloid Leukaemia in Complete Molecular Response

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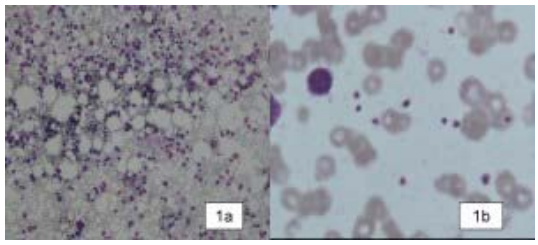
Abstract :
Chronic myeloid leukaemia is a clonal haematopoietic disorder caused by reciprocal translocation of chromosomes 9 and 22 . Imatinib , a small molecule tyrosine kinase inhibitor, targeting BCR-ABL tyrosine kinase is the first line treatment of CML. Myelosuppression is a common adverse effect of imatinib usually seen in the initial 2-4 weeks of treatment. However, severe anemia in a patient in cytogenetic and molecular response is rare . Here we present a case who developed persistent and severe anemia with imatinib after 5 years of treatment and after attaining complete molecular responseEvaluation of anaemia failed to reveal any other cause and withdrawal of imatinib led to improvement in anemia, hence implicating the drug in the causation of anaemia. The case highlights the need for constant monitoring of adverse effects even in commonly prescribed drugs after several years of treatment .
Keyword :chronic myeloid leukemia,imatinib,anaemia



Chronic Myeloid Leukaemia(CML) is a clonal haematopoietic disorder. It is caused by a genetic defect at the stem cell level. It accounts for 15% of leukaemias. It is a triphasic disease and consists of an indolent chronic phase(CP) which is characterized by excessive proliferation of fully mature cells in the myeloid lineage. It can progress to accelerated phase(AP) characterized by increasing blasts in the bone marrow and finally to an aggressive leukaemia, when the malignant clone loses the capacity to differentiate.[1]
CML results from the reciprocal translocation of chromosomes 9 and 22 t (9: 22) forming a shortened chromosome 22 called the Philadelphia chromosome(Ph). Ph chromosome and BCR-ABL protein , which functions as a constitutively activated tyrosine kinase are found

in cells of the myeloid ,erythroid , megakaryocytic lineages , some B cells and T cells , thus establishing the stem cell origin of CML [2]CML is the paradigm of targeted therapy . Imatinib mesylate (formerly STI571) is an orally active drug targeting BCR-ABL tyrosine kinase. It also inhibits stem cell factor(c kit) and platelet derived growth factor. It was approved by U.S. Food and Drug Administration in 2001 as first line treatment in Ph positive CML in all stages[3] It is also approved in gastrointestinal stromal tumour(GIST) , systemic mastocytosis, idiopathic hypereosinophilic syndrome, dermatofibrosarcoma protuberans[4,5] Myelosuppression is a .common adverse effect of imatinib in CML patients within the first 2-4 weeks of treatment[6]. However , severe anemia in a patient in complete molecular response(CMR) after five years of treatment, is rarely reported in literature.

Case:

A 25 year old male was diagnosed as a case of CML in CP in December 1999 and he was treated with hydroxyurea from January 2000 to june 2000 and with interferon from june 2000 to December 2001 by a qualified haematologist. . He reported to our institute in December 2001 and the diagnosis of CML was confirmed by cytogenetic study of bone marrow demonstrating the Philadelphia chromosome(Ph).His complete blood count(CBC) at presentation showed the following values: Hb : 14.5 g/dl ,Total White blood cell count(WBC) : 6800/mm3, Platelet count : 4.67lakh/mm3 His differential count and bone marrow aspirate at presentation were normal. His clinical examination did not reveal any abnormal finding and there was no palpable splenomegaly.He was diagnosed as CML in CP(low risk Sokal score) and was started on imatinib mesylate 400 mg/ day from January 2002 under the Gleevec International Patient Assist Programme(GIPAP) .He was in complete haematologic response (CHR) at the time of starting Imatinib. He was documented to be in complete cytogenetic response(CCyR) in May 2003, that is, within seventeen months of starting imatinib . His haemoglobin (Hb) level till that time ranged from 13-14 g/dl and he did not have any adverse reaction to imatinib except mild myalgia during the initial 6 months. He was continued on imatinib 400 mg / day and on completion of 2 years of treatment , his BCR- ABL transcript level by Real Time Quantitative Polymerase Chain Reaction(RTPCR) was 0. 42%. He attained major molecular response (MMR) in May 2005 (BCR ABL transcript 0.04%) and his BCR ABL transcript level is 0% since March 2007(CMR). His Hb level dropped to 7.9 g/dl in March 2007. His TWBC was 5000/mm3 and platelet count was 2.12 lakh/ mm3.

He underwent complete evaluation for anaemia.. His differential count showed neutrophils 60% lymphocytes 37% and eosinophils 3%. Peripheral smear study was suggestive of normocytic normochromic anemia.(fig 1b) Serum iron was 140 microgram/ dl , serum ferritin was 330 mirogram / L and Total Iron binding capacity was 325 microgram/ dl, hence excluding iron deficiency anemia. His stool was tested for occult blood and was reported as negative. He underwent upper gastrointestinal endoscopy and colonoscopy which were reported as normal. His vitamin B12 and Folic acid levels were within normal range. His reticulocyte index was 2. . His bone marrow aspirate did not reveal any abnormality except mild hypocellularity (fig 1a) Bone marrow iron stores was reported as 3+. Coombs test was negative and abdominal imaging was also normal.

As he was asymptomatic and the anemia did not interfere with his activities of daily living (ADL)., he was continued on imatinib 400mg/ day.

However, in November 2011 , he presented with a Hb level of 5.8 g/dl(severe anemia.) He was transfused with packed red cells and started on erythropoietin and iron supplements. His anemia failed to respond to 2 months of erythropoietin therapy and haematinics and he required repeated blood transfusions. He continued to be in MMR throughout this period. Erythropoietin was discontinued and he was asymptomatic except for mild exertional dyspnea. (New York Heart Association Class ii). He was advised discontinuation of imatinib for 2 weeks and his Hb level increased to 8 g/dl from 6 g/dl , hence implicating imatinib in the causation of anemia. However , in view of excellent disease control(he is in CMR since March 2007) and mild symptoms , imatinib was continued at 400mg /day with close Hb monitoring and blood transfusions as and when required. He was advised change of drug to nilotinib ,but the patient declined on account of financial constraints. He continues to have low Hb levels ranging from 6-7 g/dl without any other adverse effect and normal TWBC and platelet counts throughout the entire treatment period .He was last reviewed in September 2012 and CBC revealed Hb of 6.4 g/dl , Total WBC 4100/mm3 and platelet count of 1.01 lakhs / mm3. He was in CMR with a BCR ABL transcript level of 0 %.till that time and is continuing imatinib presently.

Discussion:

Myelosuppression can occur in upto 50% of CML patients treated with imatinib . Anemia is reported in 68% newly diagnosed CML patients[6]. Grade ¾ neutropenia and thrombocytopenia are reported in 35% and 22 % of patients respectively. However , anemia usually occurs in the initial 2-4 weeks of initiating imatinib in accelerated and blast phase and a little later in chronic phase.[6,7] Ph + stem cells are mostly responsible for haematopoiesis in CML patients. As imatinib targets BCR -ABL, thus causing suppression of the malignant clone ,myelosupression is expected in the initial phase of treatment with this drug. But the patient in this case had a normal haemoglobin level during the initial treatment period Interestingly, his Hb levels ranged from 13-14g/dl even when he had not attained cytogenetic response .However, his Hb level started falling drastically once he attained complete molecular response.

Anemia developed as a delayed effect subsequent to his attaining CMR and after completion of 5 years of treatment without any major adverse effect. Moreover , anemia in this patient was severe, requiring blood transfusions and causing NYHA class 2 dyspnea.(table 1)Factors associated with increased probability of development of anemia with imatinib are a starting Hb level less than 12 g/dl, age more than 60 years, female gender, higher dose, intermediate or high risk Sokal score[8]. Our patient had none of these risk factors. Moreover, the same authors reported that erythropoietin is a safe and effective treatment in imatinib induced anemia and achieved increase in Hb by > 2 g/dl in 68% of the patients. Also, anemia was associated with a trend towards inferior survival and lower probability of attaining Complete cytogenetic response[8]. Our patient, on the contrary, failed to respond to erythropoietin. Moreover, he continues to be in CMR despite severe anemia and occasional drug interruptions for the same. This is in concordance with the observation that anemia may

not affect outcome in CML[9] The rise in the hemoglobin level following withdrawal of imatinib for a brief period and the meticulous exclusion of other causes of anemia implicates this drug in the causation of anemia noted in this case. Imatinib related agranulocytosis has also been reported in a similar situation , when the patient was in complete cytogenetic remission. Moreover myelosuppression is also reported in patients with GIST who have normal haematopoiesis. [10] This suggests that imatinib related myelosuppression may have more than one mechanism in CML patients. The stem cell factor (c-kit) , also inhibited by imatinib is considered essential in the expansion of human hematopoietic stem cells and may have a role to play in myelosuppression [11] It is not uncommon for CML patients to develop anemia. But severe anemia occuring in a patient in CMR following 5 years of imatinib is a rare phenomenon. Indications of imaitinib and other tyrosine kinase inhibitors are expanding. As a result, we may come across more such cases in the future. Hence,. a comprehensive analysis of the various mechanisms involved in myelosuppression with this now commonly prescribed drug is the need of the hour .It is also necessary to find effective strategies to deal with such adverse effects in order to avoid treatment interruptions that may compromise long term outcome and quality of life in these ever increasing number of patients being treated with imatinib

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figure legends

Table 1: chronological trend of Hb values and BCR-ABL status

date	Hb	WBC	Platelet count	BCR-ABL
7/12/2001(at presentation)	14.5	6800	2.67	Ph+
1/2/2002(1 monthafter starting imatinib)	13.4	6300	2.95	
17/7/2004	13	5800	2.11	Ph-ve(CCyR)
12/2/2005	11.9	5000	2.10	0.04%(MMR)
10/2005	10	5100	2.12	0.005%
10/3/2007	7.9	5000	2.01	0%(CMR)
12/10/2007	6.9	4100	1.28	0%
16/11/2009	6	8100	2.23	0%
1/5/2010	5.8	4300	1.50	0%
12/3/2011	6.4	8000	1.62	0%
7/8/2012	6.4	4100	1.34	0%