Print ISSN 2319-2003 | Online ISSN 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20141013

Case Report

Imatinib resistance in chronic myelogenous leukemia: an emerging challenge

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Received: 19 July 2014
Accepted: 08 August 2014

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ABSTRACT

Resistance to imatinib is a significant clinical issue, and the underlying mechanism of this resistance is multifactorial. The efficacy of imatinib in chronic myeloid leukemia (CML) in achieving a high remission rate and improving prognosis has seriously been challenged by the development of mutants of BCR-ABL gene, which resist the action of imatinib, which is a tyrosine kinase inhibitor. We present here a case of a 35-year-old male, a known case of CML on imatinib therapy, the patient eventually landed in blast crisis and succumbed to the disease and secondary infections.

Keywords: Chronic myeloid leukemia, Imatinib resistance, blast crisis

INTRODUCTION

Imatinib resistance in BCR-ABL positive patients is rare to be seen. The causes of resistance may be many. It is only 13 years since imatinib has been started as the first-line treatment for chronic myelogenous leukemia (CML), and imatinib resistance mutants of BCR/ABL are detected in the majority of cases.

CASE REPORT

A 35-year-male patient reported in July 2013 with complaints of abdominal pain, fever and cough with expectoration. Patient was a known case of CML, diagnosed 20 months back. At presentation, BCR-ABL translocation (Philadelphia chromosome [Ph+]) was found in 98% of cells and hence he was started on imatinib 400 mg daily. On admission, he had pallor, splenomegaly and bilateral basal crepts in chest. The complete blood count (CBC) showed marked leukocytosis and anemia. Bone marrow aspiration showed markedly hemodiluted marrow with no visible marrow fragments. Bone marrow trephine biopsy was suggestive of fibrotic changes in bone marrow. His chest X-ray showed a bilateral basal consolidation and hence he was started with antibiotics and hydroxyurea in view of the increasing total leukocyte count (TLC) (43500/cmm) and basophil counts (19%) in peripheral blood. After his chest infection had been controlled, he was kept again on imatinib 400 mg OD as peripheral blood was showing increased immature myeloid precursor cells along with blast cells. Peripheral blood QBCR-ABL by reverse transcription polymerase

chain reaction was done (BCR-ABL/ABL 0.1664). Patient responded well and went into myelosuppression and was discharged with symptomatic treatment and imatinib was continued. Patient reported after a week with poor general condition; his CBC was suggestive of increased blast cells, with increased TLC and decreased hemoglobin and platelet count. Patient eventually succumbed to the disease and secondary infections (Table 1, Figures 1 and 2).

DISCUSSION

Resistance to imatinib has emerged as a significant clinical issue, and the underlying mechanisms are multifactorial. Since its approval in 2001 for frontline management of CML, imatinib has proven to be very effective in achieving high remission rates and improving prognosis. It is an emerging problem and challenge in clinical practice. Imatinib-resistance mutants of BCR/ABL are detected in the majority of cases. While, other contributing factors are genetic background, biological features of CML stem cells, gene amplifications, silencing of tumor suppressor genes, and various pharmacologic aspects.

The balanced translocation between ABL gene in chromosome 9 with BCR gene in chromosome 22 [t (9;22) (q34;q11)], termed as Ph chromosome, is a hallmark of CML.[1] The Ph chromosome is present in more than 90% of adult CML patients, in 15-30% of adult acute lymphoblastic leukemia (ALL) and in 2% of acute myelogenous leukemia.[2] Different molecular weight isoforms are generated, based on different breakpoints and mRNA splicing. Most CML patients have a fusion protein of 210 kDa while approximately 30% of Ph+ ALL cases and few CML cases are associated to 190 kDa BCR-ABL protein.[3] CML normally progresses through three clinically recognized phases: About 90% of patients are diagnosed during the typically indolent chronic phase, which is followed by an accelerated phase (AP) and a terminal blastic phase (BP). 20-25% of patient's progress directly from a chronic phase to BP and the time course for progression can be extremely varied.

Sudden blast crisis is redefined as blastic crisis onset in a patient receiving IM, after a documented complete cytogenetic response (CCyR), in the immediately preceding bone marrow analysis and without an intervening AP.[4]

The mechanisms behind CML progression are not fully understood.[2] There are increasing evidences that Src family kinases are involved in CML progression through induction of cytokine independence and apoptotic protection.[5]

Some patients who respond well to IM may still harbor residual leukemia progenitors that are susceptible to acquisition of molecular events that underlie progression to BP.[6,7]

The discovery of the BCR-ABL mediated pathogenesis of CML provided the rationale for the design of an inhibitory agent that targets the specific BCR-ABL kinase activity.

Imatinib works through competitive inhibition at adenosine triphosphate binding site of BCR-ABL protein resulting in inhibition of phosphorylation of proteins. Around 33% patient of CML treated with imatinib, did not achieve CCyR.[8-10]

Imatinib mesylate is a selective inhibitor of ABL and its derivative BCR-ABL, as well as other tyrosine kinases. It is effective against CML: A 6 year follow-up study of phase III International Randomized Interferon versus STI571 (IRIS) study, showed that imatinib induced complete hematologic

Table 1: Hematological parameters of patient on the day of admission, day 7, day 10, day 15 and day 37.

Parameters	Day 1	Day 7	Day 10	Day 15	Day 37
HB	6.6 g%	7 g%	7.2 g%	7.1 g%	8.8 g%
RBC	2.10 mill/cmm	2.28 mill/cmm	2.26 mil/cmm	2.27 mill/cmm	2.96 mill/cmm
MCV	101.3 fl	95 fl	98 fl	94 fl	96.6 fl
Total WBC count	58,200/cmm	12,000/cmm	7000/cmm	1000/cmm	26,100/cmm
Myeloblast	18	21	04	-	21
Promyelocyte	03	03	00	-	22
Myelocyte	14	30	05	-	46
Metamyelocyte	45	11	03	-	06
Band form	05	02	05	-	01
Neutrophils	13	27	62	54	01
Lymphocyte	00	05	16	42	00
Eosinophil	01	00	02	00	01
Basophil	01	01	01	00	02
Monocyte	00	00	02	04	00
Platelets	1.36 lac/cmm	1.00 lac/cmm	1.20 lac/cmm	1.70 lac/cmm	23,000/cmm

Hb: Hemoglobin, RBC: Red blood cells, MCV: Mean corpuscular volume, WBC: White blood cell

remission in the majority (98%) of newly diagnosed patients in chronic phase of the disease and complete cytogenetic remission (CCR) in about 87% of patients.[11] Major molecular response (MMR) in the IRIS trial was defined as a >3 log reduction in transcript from baseline. Obtaining MMR was associated with significantly better long-term remission duration and progression-free survival. A minority of CML patients in chronic phase and some in advanced phases are refractory to imatinib, or they lose imatinib sensitivity over the time and experience relapse. In 2006, recommendations for definitions of failure/resistance and suboptimal response to imatinib have been proposed. Failure was defined as no complete hematologic response at 3 months, no cytogenetic response at 6 months, less than partial cytogenetic response at 12 months, less than CCyR at 18 months, or loss of complete hematologic response, CCR or acquisition of BCR-ABL mutations at any time. Suboptimal response was defined as incomplete hematologic response at 3 months; less than partial CR at 6 months, less than CCyR at 12 months and less than MMR at 18 months, or acquisition of cytogenetic abnormalities in Ph+ cells, mutations of BCR-ABL or loss of MMR at any time.[12] Our patient also showed resistance after 20 months of therapy and went into blast crisis after CCyR.

Despite the obvious success of imatinib therapy, the IRIS study at 5 years follow-up showed imatinib failure: Imatinib discontinued in 31% of patients, with an estimated resistance (lack or loss of response) of 14%.[11] The expected annual rate of treatment failure after the initiation of imatinib therapy was 3.3% in the 1st year, 7.5% in the 2nd year, 4.8% in the 3rd year, 1.5% in the 4th year and 0.9% in the 5th year. The corresponding annual rates of progression to AP or BP were 1.5%, 2.8%, 1.6%, 0.9% and 0.6%, respectively. 40% of resistance is attributed to the emergence of clones expressing mutated forms of BCR-ABL with amino acid substitutions in the ABL-kinase domain that impair imatinib binding through either disruption of the critical contact point or by inducing a switch from the inactive to the active conformation.[13]

Apart from molecular resistance against imatinib, other mechanism that cause resistance in CML, have also been described. First, immature leukaemic cells (stem cells) may exhibit intrinsic (BCR/ABL-independent) resistance.[14] Second, a number of cellular molecules involved in the regulation of drug uptake, drug metabolism or drug efflux, may influence the bioavailability of imatinib.[15-18]

A special problem with imatinib is its marginal accumulation in the central nervous system, which is caused by low uptake through the blood-brain barrier.[19-22] The biochemical basis of poor uptake is not well-understood. One hypothesis is that the abundant expression of multidrug-resistant-1 (P-glycoprotein) in cells forming the blood-brain barrier is associated with constant drug efflux (Table 2).[21,23,24]

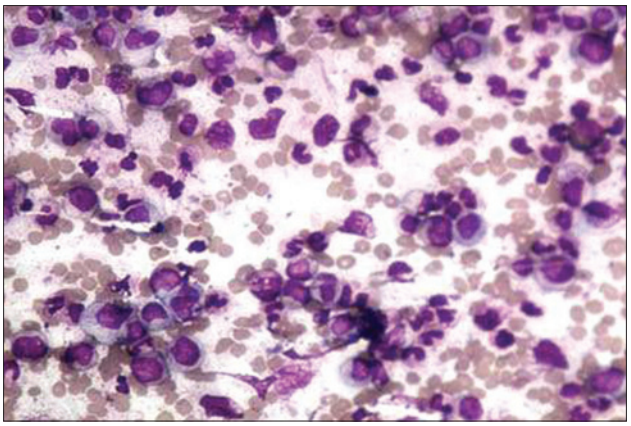

Figure 1: Peripheral smear of chronic myeloid leukemia showing blast (×400, Field's stain).

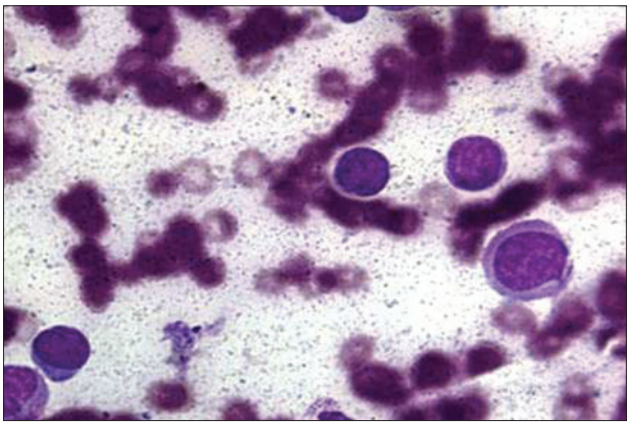

Figure 2: Peripheral smear showing myeloblast (×1000, Field's stain).

Table 2: ELN criteria for patient failure and suboptimal response to imatinib therapy.

Time on therapy (months)	Treatment failure	Suboptimal response	Optimal response
3*	No CHR	No CG response	CHR with<95% Ph+
6*	>95% Ph+ (no CyR)	36-95% Ph+ (less partial CyR)	≤35% Ph+ (partial CyR)
12	≥35% Ph+	1-35% Ph+ (partial CyR)	0% Ph+
18	≥1% Ph+	<MMR	MMR
Any	Loss of CHR Loss of CCyR mutation, CE	Loss of MMR Imatinib-sensitive mutation	Stable or improving MMR

CCyR: Complete cytogenetic response, CE: Clonal evolution, CG: Cytogenetic, CHR: Complete hematologic response, MMR: Major molecular response, Ph: Philadelphia chromosome, *These criteria were modified in the 2013 update of the National Comprehensive Cancer Network guidelines, ELN: European leukemia net's

CONCLUSIONS

Rigrous monitoring is essential during imatinib therapy as residual subclones susceptible to acquisition of new molecular events might emerge, resulting in a sudden progression of the disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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doi: 10.5455/2319-2003.ijbcp20141013
Cite this article as: Khandelwal A, Kawatra M, Bhandari V, Yeshwante PS. Imatinib resistance in chronic myelogenous leukaemia: an emerging challenge. Int J Basic Clin Pharmacol 2014;3:908-11.