Central Nervous System Blast Crisis in Chronic Myeloid Leukemia on Imatinib Mesylate Therapy: Report of Two Cases

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Abstract Chronic myeloid leukaemia is a chronic myeloproliferative disorder characterised by a reciprocal translocation between chromosomes 9 and 22 and thereby formation of the Philadelphia chromosome. Imatinib mesylate (STI-571) is a potent and selective inhibitor of BCR-ABL tyrosine kinase and has emerged as a treatment of choice in chronic myeloid leukaemia (CML) patients in chronic phase. It has shown activity in CML patients in the chronic phase or blastic phase. However there is poor penetration of the central nervous system (CNS) by the drug or its active metabolites. Therefore the CNS acts as a sanctuary site for malignant cells for CML patients treated with Imatinib. We report cases of two CML patients on Imatinib therapy, who were in haematological remission but developed CNS disease.

Keywords Chronic Myeloid Leukaemia · Central Nervous System · Blast Crisis · Imatinib

Introduction

Chronic myeloid leukaemia (CML) is a chronic myeloproliferative disorder characterised by a reciprocal translocation between chromosomes 9 and 22 resulting in the formation of the Philadelphia chromosome which is the

hallmark of this malignancy [1]. It has a triphasic evolution in which an initial chronic phase is followed after a period of 4–5 years by a phase of acute leukaemia or the blastic phase. Although majority cases of blastic transformation is characterised by increased blast cells in bone marrow and blood, some proportion of CML cases develop extramedullary disease caused by infiltration of blast cells [1]. This extramedullary blast crisis can involve lymph nodes, skin and soft tissues, serosal surfaces, bone, gastrointestinal and genitourinary tract. However CNS as a site of extramedullary blast crisis is rare [1, 2].

Imatinib Mesylate (STI-571) is a potent, selective Bcr-Abl tyrosine kinase inhibitor. It has emerged as the treatment of choice for Philadelphia positive CML patients in chronic phase and who are not candidates for allogeneic hematopoietic stem cell transplantation [2, 3]. It can induce haematological response in 95% of patients and major cytogenetic response in more than 60% of CML patients [1]. It has also shown activity in the accelerated and blastic phases of CML [1, 3]. However the penetration of the drug and its active metabolites into the central nervous system (CNS) is poor [1–3]. Hence for patients who are on prolonged Imatinib therapy and continue to have complete haematologic and cytogenetic responses, the CNS may act as a sanctuary site [2, 4].

We present two cases of chronic myeloid leukaemia on Imatinib therapy presenting to our hospital with headache and vomiting.

Case Report

Case 1

A 15 year old female patient presented to our hospital with complaints of headache, vomiting and backache for past

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2–3 months. She was admitted with similar complaints 3–4 times in the past 3 months. She was diagnosed with CML in 2006 and since then she was being treated with Imatinib in dose of 400 mg per day. On clinical examination she was found to be conscious, afebrile, without pallor, icterus or edema. Cardiovascular and respiratory system examination did not reveal any abnormality and abdomen was soft without any hepatosplenomegaly or evidence of ascites. There was swelling in the upper eyelids. Central nervous system examination showed neck rigidity, bilateral plantars were in flexion with absent deep tendon reflexes. Higher mental functions were normal.

Routine haematological investigations revealed: Hb-11.6 g/dl, total WBC-5600/cumm, N 65, L-32, E 03, M 0. Platelets were normal and no atypical cells were seen on peripheral smear. Routine biochemical investigations were normal. Fundoscopy showed normal bilateral fundi. Magnetic resonance imaging (MRI) of brain showed thrombosis of posterior part of superior sagittal sinus. Lumbar puncture was done and CSF examination showed: clear appearance, protein-60 mg/dl, sugar-40 mg/dl, chloride-690 meq/l, total WBC-600/cumm, neutrophils-34% and lymphocytes-18%. There were large atypical looking cells comprising 48%, with hyperchromatic nuclei showing altered nuclear-cytoplasmic ratio and prominent nucleoli. Gram stain did not show any bacteria, and culture was sterile. Bone marrow examination and trephine biopsy did not reveal increased blasts or immature cells. A presumptive diagnosis of CML with CNS blast crisis was made.

Case 2

A 37 year old male patient was admitted with complaints of fever with chills, headache and vomiting for last 2–3 weeks, and altered sensorium for past 2 days. He was diagnosed with CML in 2005, and was being treated with Imatinib 400 mg OD for past 4 years. On clinical examination he was found to be afebrile but drowsy and disoriented. He had no pallor, icterus or edema. Cardiovascular and Respiratory system were normal; abdomen was soft without hepatosplenomegaly or ascites. Central nervous system examination revealed neck rigidity, bilateral plantars were in flexion. Deep tendon reflexes were absent. He developed bilateral proptosis, diminished vision, and later bilateral paraplegia.

Routine blood examination showed—Hb-11.2, Total WBC-16000/cumm, N 85%, L-12%, Myelocyte-01%, Metamyelocyte-01%, blasts were absent. Platelets were—3.2 Lacs/cumm. Fundoscopic examination showed features of papilledema. Magnetic resonance imaging brain revealed bilateral multiple small infarcts with features of meningitis.

Lumbar puncture was done and CSF showed increased protein-200 mg%, increased TWBC-500/cumm. There were increased numbers of immature cells-30%, with hyperchromatic nuclei and altered nuclear-cytoplasmic ratio admixed with lymphocytes.

Both cases were provisionally diagnosed as CML with suspected CNS blast crisis and advised to go to higher centre with more specialized facilities and care. *Case #1*: A repeat lumbar puncture and CSF examination showed increased leucocyte count of 2800 cells/cumm. CSF cytopspin showed more than 90% blasts suggestive of CNS disease. Immunophenotyping showed positivity for CD 19 (87.5%), CD 10(41%), CD 34(91%) proving them to be lymphoid blasts. Fluorescent insitu hybridization (FISH) studies showed 98% fusion positivity. *Case #2*: CSF cytopspin showed 60% blasts suggestive of CNS involvement. Immuno phenotyping showed positivity for both myeloid and lymphoid antigens.

As both patients did not have HLA matched sibling donors, bone marrow transplantation was not a possible. The dose of Imatinib was increased to 600 mg once daily. six cycles of triple intrathecal chemotherapy and cranial radiotherapy were also given in both cases. At the time of this report, Case 1 is lost to follow up; Case #2 died three months later due to CNS disease (Figs. 1, 2).

Discussion

Imatinib Mesylate (STI-571) is a molecularly targeted agent that plays an important role in the treatment of Philadelphia chromosome positive leukemias through potent and selective inhibition of the Bcr/Abl tyrosine kinase. It has become the treatment of choice of CML in chronic phase especially for patients for whom allogeneic stem cell transplantation is not an option [2, 3]. It has also

Fig. 1 CSF cytology: showed groups of small immature cells with enlarged hyperchromatic nuclei

Fig. 2 CSF cytology: shows rounded mononuclear immature cells with hyperchromatic nuclei suggestive of blasts

shown activity in CML patients in the accelerated phase or blast crisis [1]. However several studies [5, 6] have shown that the penetration of the drug and its metabolites into the CNS is poor. Wolff et al. studied the effect of chronic treatment with Imatinib at therapeutic doses in mice reconstituted with Bcr-Abl transduced bone marrow cells [4]. They found that though Imatinib excellently controlled the CML like illness, but many of the mice unexpectedly developed progressive neurological deficits due to leukaemic cell infiltration of meninges and brain after 2–4 months of imatinib treatment thereby suggesting that there was inadequate penetration of the drug across the blood brain barrier into the CNS [4]. They analysed CSF concentration of Imatinib and found that it was less than 1% of plasma concentration and one-third of the concentration required to achieve 50% inhibition of cellular Bcr-Abl related tyrosine phosphorylation [4]. Neville et al. also studied the plasma and CSF pharmacokinetics of imatinib after administration in nonhuman primates and found that there is limited CSF penetration of Imatinib following per oral and intravenous administration [5]. Petzer et al. reported the low penetration of orally administered STI-571 in CSF in the human studies for the first time in 2002 [6]. Central nervous system relapses have also been reported in CML patients receiving chronic per oral imatinib after successful attainment and maintenance of systemic remission [7]. Dai et al. found that distribution of STI-571 to the brain in experimental mice is limited by a P-glycoprotein mediated efflux [8]. Pfeifer and Wassmann reported that approximately 12% of patients with relapsed or refractory Philadelphia positive leukemias receiving single agent Imatinib developed CNS leukaemia [9].

Though several case reports of CNS blast crisis in CML patients on Imatinib have been published from west

[1, 10, 11], only limited Indian case reports are available [2, 12]. On reviewing the literature it was found that in several studies [2, 8, 12], headache, vomiting were the common presenting features of CNS involvement and was seen in both our patients.

Thus in conclusion, one should be aware of the possibility of CNS relapse in CML patients on imatinib even if they have achieved hematological and cytogenetic remission. Therefore appropriate strategies and treatment protocols need to be developed to prevent and treat the CNS relapses that may occur in CML patients on treatment with Imatinib. Moreover, headache and vomiting in a CML patient who is on imatinib therapy should not be taken lightly as this may signal a possible CNS blast crisis.

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