Prophylaxis of central nervous system leukemia: a case of chronic myeloid leukemia with lymphoid blast crisis treated with imatinib mesylate

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Background: **Chronic myeloid leukemia (CML) in blast crisis has a dismal prognosis. Imatinib mesylate (IM) is a new drug which has been shown to induce complete hematological remission in 55% and complete cytogenetic response in 22% of the patients with CML in blast crisis.**

Methods: **A child with CML in lymphoid blast crisis was diagnosed by complete hematological and bone marrow examination. There was no central nervous system (CNS) leukemia at presentation. The child was treated with IM at a daily dose of 400 mg.**

Results: **The child showed remission after IM administration for 28 days and remained in remission till 59 days. On day 59 she experienced headache and vomiting. Results of cerebrospinal fluid taken for cytopathology showed CNS leukemia. MCP 841 protocol for ALL and weekly intrathecal triple therapy (ITT) was given.**

Conclusions: **Along with IM treatment in patients with CML in blast crisis, weekly ITT with hydrocortisone, cytosine arabinoside and methotrexate should be recommended to prevent CNS involvement.**

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Key words: **blast crisis;**
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Introduction

The management of chronic myeloid leukemia (CML) has improved since imatinib mesylate (IM) was discovered and approved by the FDA of USA for use in adults with CML in chronic phase, accelerated phase and blastic phase.[1] Phase I studies in children suggest that IM is well-tolerated and has limited toxicity.[2] We report a case of CML in lymphoid blast crisis treated with IM alone.

Case report

An 8-year-old girl was referred to our department with chief complaints of joint pain for 3 months, progressive abdominal distension and intermittent moderate fever, without chills, rigor, night sweats in the last 2 months.

On examination, she looked pale and both cervical and axillary lymph nodes enlarged. Distention of abdomen was observed. Her liver was palpable 6.0 cm below the right costal margin (span 9.0 cm), non-tender, firm in consistency and with smooth surface. The spleen was massively enlarged, 20-22 cm along its axis, extending down to the right iliac fossa, firm in consistency and non-tender. There was no ascites.

Complete blood count showed hemoglobin 5.8 g/dl, white blood cell count 31×10^9/L and platelet count 3.05×10^9/L. The Jenner-Giemsa staining of peripheral blood smears showed that 80% of blast cells were positive for immunophenotype markers CD10 and CD20, suggesting an acute B-lineage lymphoblastic leukemia. The peripheral smears also showed myelocytes and metamyelocytes, suggesting an underlying CML. The Bcr-Abl fusion gene was positive shown by the real-time polymerase chain reaction analysis. No blasts were discovered in cytopathological examination in cerebrospinal fluid (CSF). CML in lymphoid blast crisis was diagnosed and MCP 841 protocol for the treatment of acute lymphoblastic leukemia (ALL) was considered. But due to the financial problems, she failed to have the treatment for ALL. The good remission rate for

IM treatment causing a major cytogenetic response in 13.5% (9.6%-18.2%) and a complete cytogenetic response in 5% of cases of myeloblastic crisis in CML[3,4] prompted us to treat her with IM. The patient was diagnosed as having CML in chronic phase by bone marrow examination and cytogenetic study. She had already been treated with hydroxyurea for 39 days before referring to our hospital. IM (Cap. Veenat, Natco Pharma Ltd.) was given for a period of 1 month at a daily dose of 400 mg. Clinically, abdominal distension was decreased, organomegaly decreased, and pallor improved. The blasts in the peripheral blood disappeared. Bone marrow smear showed only 1%-2% of blasts and bone biopsy revealed that there was no increase in blasts, which confirmed hematological remission of acute leukemia, with CML in chronic phase. Capsule Veenat treatment was continued even after she had hematological remission.

No HLA matched donor could be found yet. So allogeneic stem cell transplantation was not possible. She was kept in remission for 59 days until she experienced acute headache and vomiting. She was readmitted with a diagnosis of suspected involvement of the central nervous system (CNS).

At this admission, her hemoglobin was 9.1 g/dl, total leukocyte count was 4.4×10^9/L, and platelet count was 32×10^9/L. There was neither lymphadenopathy nor hepatosplenomegaly. Bone marrow examination and bone biopsy showed the girl was still in complete remission and in the chronic phase of CML. Cytogenetic and molecular studies were not repeated at this time. CSF cytopathology, however, revealed blast cells. She was given MCP 841 protocol for acute lymphoblastic leukemia and weekly injections of intrathecal triple therapy (ITT) with hydrocortisone, cytosine arabinoside and methotrexate for CNS leukemia. At the end of 4 weeks, the repeated CSF cytopathology showed CNS leukemia. Poor prognosis was explained to her father who decided to abandon chemotherapy.

Discussion

A girl with CML in chronic phase was diagnosed and treated with hydroxyurea for 39 days before referring to our hospital. On admission, she was in lymphoblastic crisis. After molecular studies confirmed the diagnosis of CML, IM was given. Blasts disappeared and she was in remission after the treatment with IM for 1 month and kept in remission for 59 days when she presented with CNS symptoms and meningeal leukemia was diagnosed with blast cells in the CSF. At this time she was still in complete hematological remission and bone marrow also showed remission. In CML patients in blast crisis, about 60%-70% of them had myeloblastic blast cells and about one third had blast cells with lymphoid blast transformation. Generally, these cells expressed as a phenotype corresponding to an early B cell.[5,6] In our patient, lymphoid blast cells were of B-lineage.

Lymphoid crisis is more sensitive to chemotherapy than myeloid crisis, with a complete remission being achieved in about 60% of patients with an ALL type regimen.[7] In our patient MCP 841 protocol for ALL therapy was refused because of financial problems, and IM was used in view of its good response in blast crisis in CML. Kanvinde et al reported a 12-year-old child who was treated with IM for lymphoid blast crisis for 6 months, and she achieved complete cytogenetic and molecular remission 6 months later. The toxicity of IM was minimal and was well tolerated by the patient (personal communication).

Champagne et al[2] treated 10 children with Philadelphia chromosome positive ALL with IM and evaluated for morphologic responses. Seven achieved remission in bone marrow. Leis et al[8] reported isolated CNS relapse in 5 (20.8%) out of 24 patients with CML. Two of the five patients had CML in lymphoid blast crisis. At the time of CNS relapse, these two patients were still in complete remission in peripheral blood and bone marrow similar to our patient.[8] The median time of CNS relapse was 32 days in the reported series (range 23-100 days),[8,9] while in our patient the remission period was 59 days, suggesting that IM may not have a good penetration into the cerebrospinal fluid.[8,10] Therefore, in view of isolated CNS relapse we consider that CNS prophylaxis is required if IM is used in the treatment of blast crisis in CML.

Our patient tolerated IM well without any side effects. The toxicities were observed in <5% of cases, mostly grade 1 or 2 and characterized by nausea, vomiting, fatigue, diarrhoea and reversible increase in serum transaminases.[2]

The experience of Leis et al[8] and our present study suggest that if weekly prophylaxis with ITT had been given, CNS leukemia may have been prevented. Pfeifer et al[11] treated patients of acute lymphoblastic leukemia with Philadelphia chromosome and found that 13 adult patients developed CNS leukemia, and that meningeal leukemia did not occur in the patients who had received prophylactic cranial irradiation. Thus, they recommended CNS prophylaxis routinely if IM was used as a monotherapy.

We recommend 10-12 doses of ITT, which is given for CNS prophylaxis in any protocol for the treatment of ALL/lymphoma.

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References

1 FDA Approves Gleevec for leukemia treatment. FDA Consum 2001;35:6.
2 Champagne MA, Capdeville R, Kralio M, Qu W, Peng B, Rosamilia M, et al. Imatinib mesylate (ST1571) for treatment of children with philadelphia chromosome—positive leukemia: results from a children's oncology group phase I study. Blood 2004;104:2655-2660.
3 Kantarjian H, Sawyers C, Hochhaus A, Guilhol F, Schiffer C, Gambacorti-Passerini C, et al. Haematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002;346:645-652.
4 Bond M, Bernstein ML, Pappo A, Schultz KR, Krailo M, Blaney SM, et al. A phase II study of imatinib mesylate (Glivec) in patients with relapsed or refractory philadelphia chromosome positive acute lymphoblastic leukemia. Blood 2002;100:1965-1971.
5 Griffin JD, Todd RF 3rd, Ritz J, Nadler LM, Canellos GP, Rosenthal D, et al. Differentiation patterns in the blastic phase of chronic myeloid leukemia. Blood 1983;61:85-91.
6 Bakhshi A, Minowada J, Arnold A, Cossman J, Jensen JP, Whang-Peng J, et al. Lymphoid blast crises of chronic myelogenous leukemia represent stages in the development of B-cell precursors. N Engl J Med 1983;309:829-834.
7 Derderian PM, Kantarjian HM, Talpaz M, O'Brien S, Cork A, Estey E, et al. Chronic myelogenous leukemia in the lymphoid blastic phase: characteristic, treatment response and prognosis. Am J Med 1993;94:69-72.
8 Leis JF, Stephan DE, Curtain PT, Ford JM, Peng B, Schubach S, et al. Central nervous system failure in patients with chronic myelogenous leukemia lymphoid blast crisis and philadelphia chromosome positive acute lymphoblastic leukemia treated with Imatinib ST-1571. Leuk Lymphoma 2004;45:695-698.
9 Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Eng J Med 2001;344:1038-1042.
10 Bornhauser M, Jenke A, Freiberg-Richter J, Radke J, Schuler US, Mohr B, et al. CNS blast crisis of chronic myelogenous leukemia in a patient with a major cytogenetic response in bone marrow associated with low levels of Imatinib mesylate and its N-desmethylated metabolite in cerebrospinal fluid. Ann Hematol 2004;83:401-402.
11 Pfeifer H, Wassmann B, Hofmann W-K, Komor M, Scheuring U, Bruck P, et al. Risk and prognosis of central nervous system leukemia in patients with phildelphia chromosome-positive acute leukemias treated with Imatinib mesylate. Clin Cancer Res 2003;9:4674-4681.

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