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Case Report

Childhood Chronic Myeloid Leukemia Presenting with Hyperleukocytosis and Massive Splenomegaly

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Abstract

The diagnosis of Chronic Myeloid Leukemia (CML) during childhood is a rare event. Consequently, there are no fixed guidelines for the management of CML in childhood. After the introduction of Tyrosine Kinase Inhibitors (TKIs), CML patients are experiencing long-term survival with an excellent quality of life. Currently, the role of Hematopietic Stem Cell Transplantation (HSCT) in CML patients is limited to certain situations. We report a 14 year old girl with CML who presented to King Khalid University Hospital (KKUH) in Riyadh with massive splenomegaly and hyperleukocytosis requiring cytoreductive therapy and 4 sessions of leukapheresis to control her excessively elevated leukocyte count. Thereafter, the patient received imatinib then she was shifted to dasatinib after becoming intolerant to the first TKI. Later on, the patient achieved major molecular response of her CML and over the last one year, she has been having regular follow up at King Fahad Specialist Hospital (KFSH) in Dammam, Saudi Arabia.

Keywords: Chronic myeloid leukemia; Childhood; Tyrosine kinase inhibitors; Hyperleukocytosis; Leukapheresis

Introduction

CML is a clonal myeloproliferative disease of the pluripotent hematopoietic stem cells characterized by a reciprocal translocation t (9,22) (q34;q11) which forms the Philadelphia chromosome and creates the novel fusion gene bcr-abl [1,2]. CML is a triphasic disease having a chronic phase, an accelerated phase and a blast cell crisis phase [1]. There are 3 different forms of CML: an adult form, a juvenile form and an infantile or congenital form [3]. Etiological factors that are associated with the evolution of CML include ionizing radiation, familial predisposition, Down syndrome, renal transplantation and human immunodeficiency virus infection [4]. CML is diagnosed by fluorescent in situ hybridization, and real time, quantitative, polymerase chain reaction (RT-Q-PCR) for the BCR-ABL transcript. Monitoring the response to TKI therapy is usually performed by measuring the level of BCR-ABL transcript by RT-Q-PCR at three monthly intervals [1,5].

Case Presentation

In November 2014, a 14 year old Saudi girl presented to KKUH in Riyadh with fatigue, dragging sensation in the abdomen, exertional dyspnea and loss of 5 kilograms (kg) of her weight over 6 months. Her physical examination revealed pallor, huge splenomegaly with the tip of the spleen touching the right iliac bone, clear chest, impalpable liver and no external palpable lymphadenopathy. There were no neurological deficits or manifestations of respiratory distress. Her Complete Blood Count (CBC) showed: White Blood Cell (WBC) count: 683×109/liter (L), Hemoglobin (Hb): 5.8 gram/deciliter (g/dL) and Platelet Count (PLT): 317×109/L. Her renal, hepatic and coagulation profiles were all within normal limits. Her peripheral blood film revealed hyperleukocytosis with myelocytes, promyelocytes and metamyelocytes. Bone marrow examination showed a hypercellular marrow with left shift of the myeloid series, without excess of blast cells and no significant fibrosis. Cytogenetic analysis revealed the presence of Philadelphia chromosome and molecular testing for BCR-ABL p210 transcript by RT-Q-PCR was 100% on the International Scale (IS). After establishing the diagnosis of CML, the patient was admitted to the Intensive Care Unit (ICU) to keep her under close observations. In the ICU, the patient received: (1) Intravenous (IV) fluids, correction of electrolytic disturbances and allopurinol, (2) Cytoreductive therapy with hydroxyurea 50mg/kg/day and 4 sessions of leukapheresis over 4 days and (3) Imatinib treatment after confirmation of the Philadelphia chromosome positivity. Mild Tumor Lysis Syndrome (TLS) features were encountered. After decreasing her WBC count to below 100×109/L, she received two units of packed red blood cells to correct her anemia. Thereafter, the patient was shifted to the hematology ward, her hydroxyurea was discontinued and she was maintained on imatinib 400 mg/day. One week after her hospital admission, she was discharged on imatinib.

Three months after the diagnosis of her CML, the patient was seen at the outpatient clinic, her spleen was only 2 centimeters below costal margin, her blood counts were all within normal limits and BCR-ABL transcript was 0.34% on IS. She was continued on imatinib and given new follow up appointment. Three months later, the patient started to experience intolerance to imatinib, so she was shifted to dasatinib. Thereafter, the patient moved to Dammam to have further follow up at KFSH.

In October 2015, she was seen at the hematology clinic at KFSH. She was asymptomatic; her physical examination revealed no abnormality and her spleen was impalpable. Her CBC showed WBC of 5.3×109/L, Hb of 11.1 g/dL and PLTs of 136×109/L with neutrophils of 3.7×109/L. Her BCR-ABL transcript by RT-Q-PCR was 0.0027%

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on the IS. She was maintained on dasatinib and she was given new follow up appointment. Her clinical course at KFSH in Dammam was uneventful. She was last seen at the hematology clinic in October 2016, she was clinical stable, her blood counts were normal and BCR-ABL transcript by RT-Q-PCR was 0.0015% on the IS. No change in management was made and follow up at the hematology clinic was continued.

Discussion

CML is rare in children and it represents less than 7% of childhood leukemias [1,3-6]. Childhood CML accounts for less than 10% of all cases of CML [6]. Approximately 20% of children with CML are diagnosed incidentally. Childhood CML is more prevalent in males and approximately two thirds of children with CML are more than 10 years old [4,7]. The presenting clinical manifestations of childhood CML include asthenia, fatigue, weight loss and splenomegaly, while the predominant laboratory findings include anemia and high WBC count [1,7,8]. Compared to adult CML, the following are more commonly encountered in childhood disease: hyperleukocytosis, respiratory system involvement and more aggressive disease with poorer response to TKI therapy [3,8].

Hyperleukocytic leukemia is defined as leukemia with initial WBC count or blast cell count of > $100\times109/mm^2$ [9-14]. Complication of hyperleukocytosis include leukostasis, TLS and Disseminated Intravascular Coagulation (DIC) [9,11,12,15]. Leukostasis causes sludging of the circulating leukemic blasts in the microcirculature leading to microcirculatory dysfunction. The endothelial damage caused by leukostasis predisposes patients to neurological and respiratory complications which are associated with high mortality [9,14]. The clinical manifestations of leukostasis include headache, blurring of vision, papilledema, retinal hemorrhage, pulmonary infiltrates, respiratory failure, hearing loss, memory impairment, intracranial hemorrhage, cerebellar dysfunction, priapism in males and acute renal failure [10,16]. The urgent requirements in patients presenting with hyperleukocytic leukemia and impending leukostasis include: (1) Leukapheresis to rapidly reduce the elevated WBC and blast counts, (2) Cytoreductive therapy such as hydroxyurea and cytarabine, (3) Supportive measures aimed at preventing TLS including allopurinol and IV hydration, and (4) Targeted therapies such as TKIs in CML [4,9-15,17,18]. Rapid destruction of leukemic cells in response to cytotoxic chemotherapy causes electrolytic and metabolic disturbances that require prompt correction and certain preventive measures [9,11,14]. Leukapheresis has been used successfully to prevent the complications of leukostasis [9,10,17]. The indications for leukapheresis in CML patients include: WBC count > $200\times109/L$, priapism in males, severe retinopathy or papilledema, and pulmonary infiltrates [4].

The outcomes in CML have improved significantly after the adoption of TKI therapy [5,8,19]. Most of the adverse effects related to the use of TKIs in patients with CML occur early and are mild to moderate in severity [20]. Imatinib is the first choice therapy in children with CML [1,4,5]. It has demonstrated a good long-term safety profile, though recent findings suggest underestimation of the severity of side effects [20,21]. Although the drug is effective in the majority of children with CML, up to 25% of children have poor response to it as studies have shown that children with CML are less likely to achieve an early molecular response to imatinib compared to adults [19,22]. The adverse effects of imatinib therapy include lethargy, bone pains, weight gain, diarrhea, fluid retention, muscle cramps, skin rashes and abnormal liver function tests [4].

In children with CML treated with imatinib, the second generation TKIs can be tried in case of intolerance to or failure of imatinib therapy [1]. The second generation TKIs have shown higher response rates compared to imatinib, but they are associated with specific adverse events, some of which are irreversible [20]. Dasatinib, a small molecule inhibitor of multityrosine kinases inhibits: BCR-ABL, the SRC family of kinases, c-KIT, EPHA2 and platelet-derived growth factor receptor β at nanomolar concentrations [2]. Dasatinib pharmacokinetic parameters in children have been shown to be comparable to those in adults with rapid absorption and elimination [23]. Dasatinib dose in children is 60 mg/m^2/day orally [5]. It was approved by the food and drug administration in the United States in the year 2008 for the treatment of CML in chronic phase, CML in accelerated phase or blast cell crisis, Philadelphia chromosome-positive acute lymphoblastic leukemia and in case of intolerance to or failure of imatinib therapy [2,23]. In children with CML, dasatinib is indicated in patients experiencing intolerance to or failure of imatinib treatment [5]. The adverse effects of dasatinib include nausea, vomiting, diarrhea, headache, myalgia, arthralgia, fever, fatigue, skin eruptions, gastrointestinal or brain hemorrhage, myelosuppression, febrile neutropenia and fluid retention [2,20,23].

HSCT is the only proven potentially curative treatment for CML, but it is associated with up to 30% risk of treatment-related mortality [1,2,6,21]. Allogeneic HSCT in children with CML should not be offered upfront, but may be indicated as a second line in case of refractoriness to imatinib or even beyond due to the efficacy and improved tolerability of TKIs [6,19]. The current indications of HSCT in childhood CML are: (1) Lack of compliance with TKI therapy, (2) Adverse events encountered with all TKIs, (3) Patient choice of balancing risks of HSCT versus the probability of achieving a definitive cure, and (4) Failure of imatinib and dasatinib therapies to control CML [4,5].

The patient presented was more than 10 years old and she presented with features of aggressive disease. Her disease required ICU admission, cytoreductive chemotherapy, leukapheresis and measures to prevent TLS. Blood transfusion was deffered till the WBC decreased below $100\times109/L$ to prevent leukostatic complications. After confirming the presence of Philadelphia chromosome, imatinib therapy was commenced. When the patient encountered intolerance to imatinib, the drug was replaced by dasatinib which controlled her disease more optimally. In case our patient develops resistance or failure of dasatinib therapy, allogeneic HSCT may then be considered as a valuable and potentially curative therapeutic intervention.

Conclusion

CML presenting with aggressive features such as hyperleukocytosis and massive splenomegaly needs urgent management in the form of cytoreductive chemotherapy and leukapheresis so as to prevent complications such as leukostasis, TLS and DIC. Allogeneic HSCT is no longer the first or even the second line therapy in childhood CML.

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