Management of the Blast Crisis CML Patient

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This is a case of a patient with chronic myeloid leukemia in blast phase. The patient is a 57-year-old Caucasian woman in whom the diagnosis of chronic myeloid leukemia was established in July 2008 when during routine physical examination, she was noted to have a white blood cell count of 98. A bone marrow examination revealed chromosome translocation 9;22 in 100% of the metaphases. Her past medical history was notable for hepatitis C infection due to blood transfusion that was successfully treated with interferon and ribavirin. The patient began treatment with oral imatinib 400 mg daily and 6 months after the initiation of treatment in January 2009 had achieved a complete cytogenetic response.

In April 2009, routine monitoring found evidence of the Philadelphia chromosome in 20% of the cells by fluorescence in situ hybridization prompting an increase in oral imatinib dose to 600 mg daily. Molecular genetic analysis of the ABL kinase domain at that time found no evidence of mutation.

The change in clinical status prompted presentation to our institution in June 2009. Disease assessment at that time included peripheral blood fluorescence in situ hybridization analysis finding the Philadelphia chromosome in 8.2% of the interphase cells, and 2.2% of the cells had evidence of two Philadelphia chromosomes. Molecular genetic analysis of the peripheral blood showed BCR-ABL levels of 0.8%. The patient continued imatinib 600 mg daily and achieved a major molecular response, or MR3, in December 2009. In April 2010, the patient had severe periorbital edema, and oral imatinib was reduced to 400 mg daily. Serial molecular monitoring found a 1-log increase in BCR-ABL transcript.

The patient regained a major molecular response in April 2011. Three months later in July 2011, the patient had new symptoms of easy bruising. Laboratory analysis showed a WBC 37.8, hemoglobin 10.9, and platelets 140,000. Differential cell counts showed 39% blasts in the peripheral blood, and subsequent bone marrow examination showed 45% blasts which by immunocytochemistry expressed CD13, CD33, and CD34 consistent with myeloid blast crisis of CML. Molecular genetic analysis found translocation 9;22, trisomy 12, and translocation 3;21 with evidence of the EVI gene rearranged.

Induction chemotherapy was initiated with cytarabine and dasatinib, but her course was complicated by atrial fibrillation and acute tubular necrosis requiring management with
hemodialysis. She also developed bilateral pleural effusions requiring chest tubes. Intercurrent HLA typing found no matches in any of her six siblings but identified two potential unrelated donors who were 10/10 matches.

Unfortunately, in September 2011, bone marrow examination revealed persistent leukemia with 30% blasts. A second course of induction therapy was initiated with nilotinib, daunorubicin, and thioguanine. In October 2011, WBC was 5.3, hemoglobin was 8.1, and the platelets were 156,000. The bone marrow was hypercellular, and 5% blasts were noted. Cytogenetic analysis found normal chromosome complement in 60% of the cells, but 40% of the cells had the translocation 9;22, trisomy 12, and translocation 3;21. At that time, it was felt that she was not fit enough to tolerate allogeneic stem cell transplant, and in November 2011, she had recovered enough to consider stem cell transplant; but by December 2011 she had evidence of overt relapse with WBC of 14.3% and 34% blasts in the peripheral blood. Subsequent attempts to induce remission were unsuccessful. Treatment with nilotinib, mitoxantrone, and etoposide failed. In January 2012, the WBC was 9.5 with 21% blasts in the peripheral blood. Treatment with idarubicin, high-dose cytarabine, and dasatinib in February 2012 was complicated by bacteremia with gram-negative rods and probable fungal pneumonia. A bone marrow examination performed on day #14 was hypocellular, but by day #30, the peripheral blood had 57% blasts. Supportive management was instituted at that time with hydroxyurea, and 57 days after the initiation of the final attempted re-induction, the patient expired due to sepsis.

This case illustrates the challenges in managing patients with the blast crisis phase of chronic myelogenous leukemia. The blast crisis can occur either as a myeloid blast crisis or as a lymphoid blast crisis. The World Health Organization has defined blast crisis CML as the presence of 20% or more blasts in the blood or bone marrow evidenced as extramedullary blast proliferation or a large focus or cluster of blasts in the marrow.

The International Bone Marrow Transplant Registry defines CML blast crisis slightly differently as 30% or more blasts in the blood or bone marrow or extramedullary infiltrates of leukemic cells.

Unfortunately, there is no standard of active treatment of blast crisis CML. The National Comprehensive Cancer Center Network (NCCN) recommends clinical trials for patients with either myeloid or lymphoid blast crisis. Allogeneic stem cell transplant, however, is the only modality that has been shown to lead to cure of this condition. For patients with myeloid blast crisis, the NCCN also suggests the use of a tyrosine kinase inhibitor either alone or with regimens known to be active in treating acute myeloid leukemia followed by allogeneic stem cell transplant as a possible treatment option. For patients with
lymphoid blast crisis, treatment with a tyrosine-kinase inhibitor either alone or with regimens known to be active in acute lymphoblastic leukemia followed by allogeneic stem cell transplant has been recommended.

Each of the second- and third-generation tyrosine-kinase inhibitors has been studied in patients with blast crisis CML and has been shown to induce complete cytogenetic remissions in 10-40% of patients; typically however, the overall duration of remission is less than 1 year, and few patients are able to proceed to allogeneic stem cell transplant. The combination of tyrosine-kinase inhibitors and standard chemotherapy regimens in patients with CML in blast crisis has been modeled after the successful use of tyrosine-kinase inhibitors and acute lymphoblastic leukemia regimens in patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia. These regimens have been shown to demonstrate prolonged disease-free remissions in patients with Ph+ ALL. Unfortunately, those results have not been replicated in patients with blast crisis CML, and this condition continues to be very challenging. Fortunately with the advent of the second-generation tyrosine-kinase inhibitors, blast-phase CML is an uncommon occurrence, and data suggests that the use of second-generation tyrosine-kinase inhibitors as initial treatment may further reduce the incidence of blast-phase CML.

References


