INTRODUCTION

Philadelphia chromosome (Ph) is acquired structural chromosomal abnormality resulting from a reciprocal translocation between chromosome 9 and 22. It is characteristic of chronic myeloid leukemia but it is not only restricted to it. Ph is also frequently positive in acute lymphoblastic leukemia, but Ph positive de novo acute myeloid leukemia (AML) is a rare disease with reported incidence of less than 1% (0.6% and 0.9%) of newly diagnosed cases of AML.\(^1\)\(^2\) Outcome of Ph positive de novo AML is poor, and the median overall survival is 6 - 9 months. No standard/consensus treatment protocols are available of Ph positive de novo AML and published data is limited to few case reports only. Significant controversy exists, whether this represents a true acute leukemia or simply a presentation of chronic myelogenous leukemia (CML) in myeloid blast crisis (CML-MBC).\(^3\) What appears to be a Ph+ AML could be a CML with an asymptomatic chronic phase that never came to medical attention or had a rapid progression to the blast phase. Most patients with CML have an accelerated phase that precedes the development of blast crisis, but in 25% of patients with chronic phase CML, the onset of the blast phase is abrupt without an intervening accelerated phase,\(^4\) raising the possibility of presenting in the blastic phase of CML with a short or silent chronic phase. Clinical criteria suggested to differentiate Ph+ AML from CML-MBC include an absence of a clinical history of a hematologic disorder, lack of evidence of chronic phase or accelerated phase CML after induction chemotherapy, and a lack of clinical and laboratory features of CML, such as splenomegaly and basophilia.\(^3\) Additional cytogenetic aberrations, common to CML-MBC, such as extra copies of Ph and trisomy 8, are less common in Ph+ AML and co-existence of normal metaphases along with Ph+ metaphases at diagnosis is more characteristic of Ph+ acute leukemias than of CML-MBC.\(^5\) Return to a normal karyotype following induction chemotherapy is more common in patients with Ph+ acute leukemias, whereas the t(9;22) persists in similarly treated CML-MBC.\(^5\) We report a cases of Ph+ AML, diagnosed in November 2014 at Oncology Unit, Jinnah Hospital, Lahore. His presentation, morphologic features, cytogenetics and treatment response are discussed along with literature review.

CASE REPORT

A 24-year male university student presented with 3 months’ history of low grade on and off fever. Physical examination, apart from pallor and petechial rashes on both legs, was normal. There was no lymphadenopathy, spleen and liver was not palpable; however, ultrasound showed mild splenomegaly. Peripheral blood showed high TLC count with no basophilia. Bone marrow showed mild splenomegaly. Peripheral blood showed high TLC count with no basophilia. Bone marrow showed 25% blast cells with features suggestive of AML M2 of FAB classification. Flow cytometry confirmed the diagnosis of AML. Bone marrow cytogenetics was positive for Ph (Figure 1). Patient was treated with imatinib 400 mg daily and conventional (3+7) induction chemotherapy with daunorubicin 45 mg/m\(^2\) for 3 days intravenous bolus and cytarabine 100 mg/m\(^2\)/day 24 hours continuous infusion for 7 days. Patient did not develop any serious complications during and after induction therapy and achieved morphological complete remission (CR) after induction of chemotherapy and bone marrow did not reveal any evidence of chronic myeloproliferative disorder. Imatinib was continued and
patient was consolidated with 4 cycles of high dose Ara-C (Cytarabine 3 gram/m² morning and evening intravenous infusion on day 1, 3 and 5 of 21-day cycle). Patient remained in overall good health condition during consolidation cycles with no major chemotherapy or disease related complications except for 2 successfully managed episodes of febrile neutropenia requiring in-hospital care. Post-consolidation bone marrow examination was in CR, BCR-ABL protein by FISH was also undetectable. After completion of consolidation therapy, the patient was maintained on daily imatinib, but relapsed after 3 months of imatinib besylate maintenance and eventually died after 1 month of relapse in August 2015.

DISCUSSION

The translocation between chromosome 9 and 22 results in the formation of Ph and generates an active chimeric BCR-ABL tyrosine kinase. This chromosomal anomaly is most commonly associated with CML and precursor B-acute lymphoblastic leukemia (ALL). About 32% of bilineage leukemias are also positive for Ph. However, patients with AML bearing this translocation (Ph+ AML) have rarely been reported, which is less than 1% of all de novo AML cases.¹ ²

No standard/consensus treatment protocols are available of Ph positive de novo AML. Literature review shows that a wide range of treatment options have been tried including chemotherapy alone, chemotherapy with imatinib, imatinib alone, gemtuzumab alone or in combination with chemotherapy and allogenic stem cell transplant, but none of these options had shown sustained long-term responses; overall median survival is 9 months, which is similar to CML-MBC and other AML cases with adverse cytogenetics. Most reported cases of Ph+ de novo AML pre-date imatinib were treated with such conventional AML therapy. In one series, 4 (36%) of 11 patients treated with conventional chemotherapy regimens achieved complete responses, with a duration of 3 - 14 months and a median survival of 7 months.³ However, none of 6 patients with Ph+ de novo AML in another study treated with conventional chemotherapy achieved remission.²

The advent of imatinib has significantly changed the approach to the treatment of CML.⁵ ⁷ There is little information on the response of patients diagnosed with Ph+ de novo AML to imatinib, with only rare case reports available.⁸ Three cases of Ph+ AML treated with imatinib had sustained cytogenetic responses, including one who achieved a molecular remission lasting for 15 months.⁸ A series of 7 patients which were treated with imatinib, with 5 having transient hematologic responses only and one patient having a complete hematological response, lasting 6 months. Overall survival in patients who received allogenic stem cell transplant is reported to be 12 months.³ It has been reported that approximately half of patients with Ph+ AML attain complete remission with conventional chemotherapy and karyotype reverted to normal. Two patients reported from Pakistan, showed transient response lasting 7 months in one patient; and no response to conventional chemotherapy and imatinib in the other.⁹

The presently described patient’s clinical presentation and laboratory investigations and treatment response is consistent with other reported cases of Ph positive de novo AML. As there is no established standard treatment protocol and reports of allogenic transplant are also not encouraging, so this patient was kept on imatinib maintenance; but he relapsed after 3 months of maintenance. He remained in complete hematological remission for 8 months, which is again consistent with reports of available literature.

REFERENCES

6. Sawyers CL, Hochhaus A, Feldman E. Imatinib induces hematologic and cytogenetic responses in patients with...


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