PHILADELPHIA CHROMOSOME POSITIVE ACUTE MYELOID LEUKEMIA: A RARE HEMATOLOGICAL DISORDER: A CASE REPORT

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ABSTRACT

Philadelphia chromosome positive (Ph-positive) acute myeloid leukemia (AML) is an extremely rare and aggressive disease constituting approximately 1-3% of all de-novo AML cases. This disorder has many features distinct from chronic myeloid leukemia (CML) in blast crisis (CML-BC) and is therefore considered a distinct entity. Patients with Ph-positive AML have lower peripheral basophilia, lower bone marrow cellularity and lower myeloid/erythroid ratio. Presentation is acute with a short history and these patients are less likely to have splenomegaly. Outcome of the disease is poor and median overall survival is 6-9 months. This disease shows resistance to conventional chemotherapy protocols. We have identified two cases of Ph-positive AML amongst all de-novo AML patients diagnosed in our unit from January 2006 to December 2010. Both were treated with two courses of Cytarabine and Daunorubicin followed by Imatinib Mesylate (IM) 600 mg orally daily. Patient no. 1 did not respond to two cycles of chemotherapy as well as IM 600 mg daily and died after 5 months. Patient no. 2 had a complete hematologic response after two cycles of chemotherapy along with IM and remained in full hematological remission with IM 600 mg daily maintenance for 7 months after diagnosis. After 7 months he had a relapse and died after 2 months of relapse. Combination of AML type of chemotherapy and maintenance with IM provides short term remission while allogeneic stem cell transplant (ASCT) may achieve long term survival in a few patients.

Key words: *Philadelphia chromosome positive, acute myeloid leukemia (AML), clinico-pathological presentation*

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INTRODUCTION

Presence of Philadelphia chromosome or t (9:22) (q34:q11) is the most common and consistent abnormality seen in patients with chronic myeloid leukemia (CML). Approximately 20-37% adult patients with acute lymphoblastic leukemia (ALL) and biphenotypic acute leukemias (BAL) also have this translocation that portends a poor prognosis while presence of Philadelphia chromosome in other hematological disorders is extremely rare[1,2]. In AML, Philadelphia chromosome translocation has been reported in 1-3% of all AML cases[3-5]. Due to its rarity, majority of Ph-positive AML cases have been reported as case reports and no guidelines regarding optimal treatment are available due to lack of randomized studies in this rare disorder[6]. The largest study published to date on Ph-positive AML has reported a total of 16 cases in a 9 year study period[7]. Different groups have used various types of chemotherapy protocols, Imatinib Mesylate (IM) or stem cell transplant but all have resulted in short survival periods[4,7].

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We report two cases of Ph-positive AML diagnosed at Medical Oncology Unit, Hayatabad Medical Complex, Peshawar between January 2006 and December 2010. Their presentation, morphologic features, cytogenetics and treatment response is discussed along with literature survey on the topic.

CASE REPORT

Two patients with Ph-positive AML were identified at Medical Oncology Unit, Hayatabad Medical Complex, Peshawar since January 2006. Clinical features at presentation in both patients included pallor, bruises, fever and bone pains with

a median duration of onset of 20 days. Both our patients did not have any splenomegaly, hepatomegaly, or lymphadenopathy both clinically or radiologically at presentation. Peripheral blood basophilia was not seen in both of our patients and both patients had a normal myeloid/erythroid ratio (2:1). Cytogenetic analysis for Philadelphia chromosome showed t (9:22) in both these patients as shown in Figure 1. Demographic characteristics and hematological data at presentation of both these patients are shown in Table 1.

Immunophenotyping of both patients could not be done since they were not available at our Institute therefore the authors can not comment on whether these patients had pure myeloid lineage AML or were bilineal.

Patient no.1 did not respond to two cycles of induction chemotherapy which included Cytarabine 100 mg/m2 intravenously daily for seven days and Daunorubicin 50 mg/m2 intravenously daily for three days. After the second course of cytotoxic chemotherapy, peripheral smear and bone marrow both showed blasts > 80% and Philadelphia chromosome positivity was 100%. He was then started on IM 600 mg/day. Although his blast cell count improved initially and came down to 21% but he also developed severe thrombocytopenia and a skin rash due to IM. Dose of IM was reduced to 400 mg/day and then gradually increased to 500 mg/day along with supportive care. Patient remained in partial remission with Imatinib for three months after which his blasts started increasing once again. This patient died five months after diagnosis despite being on chemotherapy, maintenance IM and intensive supportive care.

Patient no. 2 also received two cycles of induction chemotherapy and maintenance IM as described above for patient no. 1. After first cycle of induction chemotherapy, his blast cells dropped to 10%. After cycle 2 of induction chemotherapy he achieved a complete hematological remission (CHR) upon bone marrow examination. He remained on IM 600 mg/day as maintenance therapy and remained in CHR for seven months after therapy. He had a relapse after 7 months and died 2 months after relapse. Hematological profile at presentation of both patients is presented in Table 1.

Figure 1: Cytogenetic Analysis on Bone Marrow Specimen of a Patient with AML Showing Positivity for Philadelphia Chromosome [46, XY, t (9:22) (q34; q11.2)] with translocation of Chromosomal Material between Chromosome 9 and 22 (arrows)

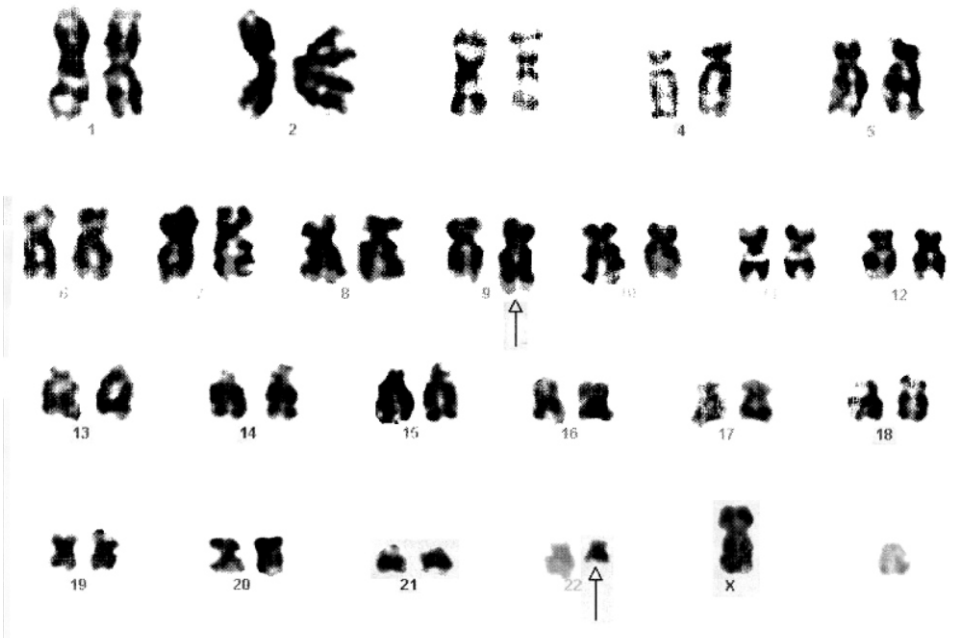

Table 1: Demographic Characteristics and Hematological Profile at Presentation of Ph-positive AML Patients.

Characteristic	Patient 1	Patient 2	Mean
Age	13 years	28 years	20.5 years
Sex	Male	Male	-
Initial hemoglobin	10 gm/dl	8.2 gm/dl	9.1 gm/dl
Initial WBC count	113000/cumm	47700/cumm	80350/cumm
Initial platelet count	65000/cumm	73000/cumm	69000/cumm
Initial BM blast count	90%	50%	70%
Initial S. LDH level	750 U/l	1560 U/l	1155 U/l
% cells Ph +ive	20/20 (100%)	05/20 (25%)	62.5%
Sub-type of AML M1	M2	-	
Peroxidase staining	Positive	Positive	-
Cytogenetics for BCR-ABL	Positive	Positive	-

DISCUSSION

Incidence of Ph-positive AML has been reported by various groups to be between 0.3-3%[4,5,7]. This difference in the incidence rate has been explained by Soupir et al on the basis of immunophenotyping[7]. In the studies that reported a higher incidence of 3%, patients with biphenotypic and bilineal AML were included in the studies[5,8]. In the studies showing a lower incidence of < 1%, patients with biphenotypic or bilineal AML were excluded and only patients with purely myeloid lineage de novo AML were included[3,7].

Care has to be exercised in order to differentiate de novo Ph-positive AML from CML patients in myeloid blast crisis or from secondary AML cases. As a general rule, patients with de novo Ph-positive AML are less likely to have additional chromosomal abnormalities (approximately 20%) compared to patients with CML with myeloid type of blast crisis (80%)[9]. At presentation, patients with Ph-positive AML will present with an acute course of the disease and history of any antecedent hematologic disorder will be absent. These patients also tend not to have splenomegaly or have only mild splenomegaly at presentation. Classic hematologic picture of chronic phase or accelerated phase CML is not present and their peripheral smear and bone marrow picture show lower incidence of basophilia, lower bone marrow cellularity and normal M:E ratio compared to patients with CML[7,10].

Ph-positive AML patients present at an early age (mid twenties) and the disease tends to run an aggressive course. In majority of cases disease is unresponsive to cytotoxic chemotherapy or even to IM[4,7,8]. Chemotherapy in addition to IM is required in these patients[11]. Case reports have shown a response to IM either alone or in combination with chemotherapy or chemotherapy followed by Imatinib maintenance or to ASCT but recurrences are common[6,11,12]. Median survival of patients has been reported to be between 3-9 months[7,8].

Our study is in concurrence with those reported in the literature with an incidence of 1% and median age of presentation of 20.5 years[4,8]. Both our patients presented with acute symptoms and did not have any preceding hematological disorder. Both of them did not have splenomegaly, hepatomegaly or lymphadenopathy either clinically or radiologically. Response to treatment of patient no. 1 was unsatisfactory with a short survival of only 05 months whereas patient no 2 responded initially to chemotherapy followed by maintenance with IM but died after nine months of diagnosis. At the time of management of these patients, Dasatinib or Nilotinib were not available commercially in Pakistan.

In conclusion, Ph-positive AML is a distinct entity with a very low incidence. It runs an aggressive course with median survival of 3-9 months despite treatment with cytotoxic chemotherapy and IM or ASCT and recurrences are common.

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