

Philadelphia-Positive Acute Myeloblastic Leukemia: A Rare Entity

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Received date: March 13, 2016; **Accepted date:** April 06, 2016; **Published date:** April 12, 2016

Citation: Gajendra S, Sahoo MK. Philadelphia-Positive Acute Myeloblastic Leukemia: A Rare Entity. J Neoplasm 2016, 1:1

Definition

Philadelphia positive (Ph+) Acute Myeloblastic Leukemia (AML) is an acute onset neoplasm of myeloblasts in which the blasts harbor BCR/ABL translocation in the absence of a clinical history of chronic phase or accelerated phase chronic myeloid leukemia (CML) and a lack of clinical and laboratory features of CML, such as splenomegaly and basophilia.

Keywords: Philadelphia chromosome; BCR/ABL; Acute myeloid leukemia

Genetics

The Philadelphia chromosome was first discovered in Philadelphia in 1960. It corresponds to shortened chromosome 22 resulting from reciprocal translocation between long arm of chromosome 9 and short arm of chromosome 22, which is designated as t(9;22)(q34;q11). This gives rise to a BCR/ABL fusion gene, that juxtaposes the ABL1 gene on chromosome 9 (region q34) to a part of the BCR ("Breakpoint Cluster Region") gene on chromosome 22 (region q11). There are two major forms of the BCR/ABL fusion gene of different sizes involving ABL exon 2 with different exons of BCR gene. Major BCR (M-BCR) resulting in b2a2 and b3a2 mRNA transcripts, p210 chimeric protein, are most commonly involved in CML patients. Minor BCR (m-BCR), e1a2 mRNA transcripts and p190 chimeric protein, are most frequently associated with Ph positive Acute Lymphoblastic leukemia (ALL) and in many patients with CML. Third less common fusion gene involving breakpoint in micro BCR (μ -BCR), e19a2 and result in p230 chimeric protein, may demonstrate prominent neutrophilic leukocytosis; these should be diagnosed as chronic neutrophilic leukaemia [1,2].

Mechanism

The ABL gene expresses a membrane associated protein, a tyrosine kinase, and the BCR-ABL transcript is also translated into a tyrosine kinase. The mutant tyrosine kinase of the BCR-ABL transcript codes for a protein that is continuously activated and subsequently activates a number of cell cycle controlling proteins and enzymes resulting in unregulated cell division. Several functional domains have been identified in the BCR-ABL protein that may contribute to cellular

transformation. In the ABL portion, these domains are the SH1 (tyrosine kinase), SH2 and actin-binding domains and in the BCR portion, they are the coiled-coil oligomerization domain comprised between amino acids (aa) 1-63, the tyrosine at position 177 (GRB-2 binding site) and the phosphor serine/threonine rich SH2 binding domain. The increased tyrosine kinase activity of BCR-ABL fusion protein results in phosphorylation of several cellular substrates and auto-phosphorylation of BCR-ABL, which in turn induces recruitment and binding of a number of adaptor molecules and proteins. BCR-ABL activates signal transduction pathways such as RAS/MAPK, PI-3 kinase, c-CBL and CRKL pathways, JAK-STAT and the SRC pathway. The major role in transformation and proliferation is played by the RAS, JUN-kinase, and PI-3 kinase pathways. Inhibition of apoptosis is thought to result from activation of the PI-3 kinase and RAS pathways, with induction through AKT of C-MYC and BCL-2. Unregulated cell proliferation with inhibition of apoptosis plays a major role in oncogenesis in Ph+ leukemias [3,4].

Epidemiology

The p210 fusion protein is characteristic of CML, occurring in about 95% of the cases and in 20% of Ph+ ALL, in which the p190 fusion protein is more frequent. The p230 is usually associated with chronic neutrophilic leukemia. The incidence of Philadelphia chromosome in Ph+ AML is approximately 0.5-3% as reported by various groups [2]. An incidence of <1% was reported in the studies where the biphenotypic and bilineal AML were excluded and only pure *de novo* cases of AML were considered. A higher incidence of 3% was reported when biphenotypic or bilineal cases were included in the studies [5]. Most of the Ph+ AML cases expressed the p210 BCR-ABL transcript which is typical of CML-MBC and few Ph+ AML cases expressed a p190 BCR-ABL transcript, which is only rarely expressed in CML-MBC.

Clinical Features

Clinical presentations are similar to that of acute myeloid leukemia. However, Ph positivity in AML is more common in adult than children.

Diagnosis of Ph chromosome (BCR/ABL translocation)

Cytogenetic and molecular analysis plays important role in the diagnosis and monitoring of the disease to assess complete cytogenetic and molecular response. Peripheral blood and bone marrow samples are examined for Ph chromosome. Conventional G banding karyotyping is the most simple and cost-effective technique and can be able to demonstrate Ph chromosome in approximately 95% of cases; however, rest of the cases require more sensitive molecular methods. In conventional karyotyping, Ph chromosome positivity is expressed as percentage of Ph+ metaphases out of all metaphases analyzed. A minimum of 20 metaphases were analyzed routinely according to ISCN guidelines. Fluorescence *in situ* hybridization (FISH) can be performed on metaphase spreads and interphase nuclei, using locus specific probes for BCR-ABL gene. In normal interphase nuclei four separate fluorescent signals i.e., two green and two red are seen. In Ph +ve nuclei, however, there are two separate signals which represent the two normal chromosomes and an orange-green doublet or a yellow signal corresponding to BCR-ABL fusion gene on chromosome 22. The more advance molecular technique as reverse transcriptase polymerase chain reaction (RT-PCR), total RNA was extracted and is reverse transcribed to make complimentary DNA (cDNA). PCR primers specific to the DNA sequences of portions of BCR/ABL were used to amplify the cDNA. The PCR products were separated by agarose gel electrophoresis and visualized by UV transillumination. The real time PCR (RQ-PCR) assay detects e1a2, e13a2, and e14a2 transcripts in a single tube and is normalized to ABL1, with BCR-ABL transcript type(s) determined by subsequent capillary electrophoretic separation of the fluorochrome labeled products. This RQ-PCR can detect residual disease in a very low level [5].

Morphology, cytochemistry and immune-phenotyping

There is no difference in morphology, cytochemistry and immunophenotyping features that differentiate it from other type of AML.

Differential diagnoses

The most important differential diagnosis of Ph+ AML is CML in myeloid blast crisis (CML-MBC). The criteria suggested to differentiate Ph+ AML from CML-MBC include: acute presentation with a short history, lack of history of previous chronic phase and also lack splenomegaly. The age of presentation of ph+ AML is earlier in comparison with CML-MBC. It also lacks peripheral blood and bone marrow basophilia and also has a lower peripheral blood maturing myeloid cell count (excluding blasts) at presentation than the CML-MBC group. The Ph+ AML has lower bone marrow cellularity and myeloid/erythroid ratio. Presence of dwarf megakaryocytes is common in CML-BC which is a rare finding in Ph+ AML. There is no significant difference in total leucocyte count, percentage of eosinophil's, or monocytes. There was

also no difference in the number of megakaryocytes or in erythroid, myeloid, or megakaryocyte dysplasia [6-8]. There is also no difference in percentage and immune-phenotyping of blasts between the two groups. Cytogenetic and molecular features can be useful in distinguishing this pathology. In CML-MBC, clonal evolution, which is defined as additional chromosomal abnormalities, occurs in 60% to 80%. The most common additional abnormalities are extra Ph chromosome, trisomy 8, trisomy 19 or isochromosome 17q. However, an additional chromosomal abnormality in Ph+ AML occurs in 25% to 55% cases. Few studies Deletion 7q (-7q) abnormalities were present in case of Ph positive AML, as demonstrated by few series. Association of mutations suppressing cell differentiation (Core Binding Factor AML) and mutations increasing cell proliferation (as FLT3 gene, KIT gene) is more frequent in Ph+ AML than in CML-MBC. Two recent studies have shown that Nucleophosmin (NPM1) is commonly mutated in AML and absent in CML-MBC, whereas ABL1 mutations are common in CML [9,10]. Another differential diagnosis is mixed phenotypic acute leukemia with t(9;22) (q34;q11.2) which can be differentiated by having dimorphic blast population as demonstrated by immune-phenotyping [myeloid as by myeloperoxidase or monocytic differentiation (any 2 of CD14, CD64, CD11c, NSE, lysozyme) with B lymphoid (CD19 with 1 of CD79a, CD10, CD22) or T lymphoid (surface/cytoplasmic CD3)] [11].

Treatment

This disease shows resistance to conventional chemotherapy protocols. Imatinib mesylate is a selective BCR-ABL tyrosine kinase inhibitor, has shown significant antileukemic activity in patients with Ph+ leukemia. Imatinib as monotherapy failed to show efficacy as induction therapy. However, when Imatinib is started after achieving complete response with AML chemotherapy, it allows in achieving a complete cytogenetic and molecular response. The doses of Imatinib reported in the literature are 400 mg and 600 mg/day. Some authors suggested as the patients are at considerable risk of meningeal leukemia during monotherapy, they should routinely receive CNS prophylaxis, cranial irradiation or intrathecal chemotherapy [12]. A combination of AML chemotherapy with maintenance of Imatinib can provides remission and a subsequent allogeneic stem cell transplant (ASCT) is the best consolidation therapy for the patients with Ph+ AML [3]. The median and the overall survival of the patients can be increased by addition of Imatinib to the conventional AML therapy followed by ASCT.

Prognosis

Induction failure and relapse is also common in Ph+ AML. Long-term survival may be achieved with HSCT as earlier as after complete remission from Imatinib and chemotherapy treatment analyzed 12 Ph+ AML patients and showed a median overall survival 24 (8-80) months and the the overall survival of 3 years was (51.4 ± 17.7%) [13].

Conclusion

The Ph+ AML is a distinct clinico-pathological entity and not a *de novo* presentation of CML-myeloid blast crisis. The most recent version of the World Health Organization (WHO) classification does not include AML with t (9;22)(q34;q11.2)/BCR-ABL1 Ph+ as an different entity. But it should be differentiates from CML-MBC as both have different clinical, morphological, cytogenetic and molecular features. A combination of AML chemotherapy followed by maintenance by Imatinib can provides complete cytogenetic and molecular response and ASCT can further provides a long term survival.

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