Leukaemia Section
Mini Review

Chronic myelogenous leukaemia (CML)

Ali G Turhan

Translational Research - Cell Therapy, Laboratory, Institut Gustave Roussy, INSERM U. 362, 1 - 39, rue Camille Desmoulins, 94805 Villejuif Cedex, France (AGT)

Published in Atlas Database: October 2000
Online updated version : http://AtlasGeneticsOncology.org/Anomalies/CML.html
DOI: 10.4267/2042/37672


This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2000 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Clinics and pathology

Disease
CML is a malignant chronic myeloproliferative disorder (MPD) of the hematopoietic stem cell.

Phenotype/cell stem origin
Evidence exists for the involvement of the most primitive and quiescent hematopoietic stem cell compartment (CD34+/CD38-, Thy1+): t(9;22) is found in myeloid progenitor and in B-lymphocytes progenitors, but, involvement of the T-cell lineage is extremely rare.

Epidemiology
Annual incidence: 10/10^6 (from 1/10^6 in childhood to 30/10^6 after 60 years); median age: 30-60 years; sex ratio: 1.2M/1F.

Clinics
Splenomegaly; chronic phase (lasts about 3 years) with maintained cell's normal activities, followed by accelerated phase(s) (blasts still 30%; blood data: WBC:100 X 10^9/l and more during chronic phase, with basophilia, a few blasts; thrombocytosis may be present; low leucocyte alkaline phosphatases; typical acute leukaemia (AL) blood data at the time of myeloid or lymphoid-type blast crisis.

Cytology
Hyperplastic bone marrow; granulocytes proliferation, with maturation; followed by typical AL cytology (see: t(9;22)(q34;q11) in ALL, t(9;22)(q34;q11) in ANLL).

Treatment
alphafIFN therapy or allogeneic bone marrow transplantation (BMT), donor leukocytes infusions.

Prognosis
Median survival: 4 years with conventional therapy (hydroxyurea, busulfan), 6 years with aIFN therapy; allogeneic bone marrow transplantation may cure the patient; otherwise, the best treatment to date associates interferon a, hydroxyurea and cytarabine.

Cytogenetics

Cytogenetics morphological
All CML have a t(9;22), at least at the molecular level (see below); but not all t(9;22) are found in CML: this translocation may also be seen in ALL, and in ANLL (see: t(9;22)(q34;q11) in ALL, t(9;22)(q34;q11) in ANLL), and the same genes are involved in the three diseases; in CML, the chromosomal anomaly persists during remission, in contrast with AL cases.

Cytogenetics molecular
Is a useful tool for diagnostic ascertainment in the case of a 'masked Philadelphia' chromosome, where chromosomes 9 and 22 all appear to be normal, but where cryptic insertion of 3' ABL within a chromosome 22 can be demonstrated.

Additional anomalies
1- May be present at diagnosis (in 10%, possibly with unfavourable significance), or may appear during course of the disease, they do not indicate the imminence of a blast crisis, although these additional anomalies also emerge frequently at the time of acute transformation;
2- These are: +der(22), +8, i(17q), +19, most often, but also: +21, -Y, -7, -17, +17; acute transformation can also be accompanied with t(3;21)(q26;q22) (1% of cases); near haploidy can occur; of note, although rare,
Chronic myelogenous leukaemia (CML) Turhan AG

Atlas Genet Cytogenet Oncol Haematol. 2000; 4(4)

is the occurrence of chromosome anomalies which are typical of a given BC phenotype (e.g. t(15;17) in a promyelocytic transformation, dic(9;12) in a CD10+ lymphoblastic BC); +8, +19, +21, and i(17q) occur more often in myeloid -rather than lymphoid- blast crises and apparent t(V;22) or t(9;V), where V is a variable.

**Variants**

Chromosome, are found in 5-10% of cases; however, 9q34-3′ABL always joins 22q11-5′BCR in true CML; the third chromosome and breakpoint is, at times, not random. In a way, masked Philadelphia chromosomes (see above) are also variants.

**Genes involved and proteins**

**ABL**

**Location**

9q34

**DNA/RNA**

Alternate splicing (1a and 1b) in 5′.

**Protein**

Giving rise to 2 proteins of 145 kDa; contains SH (SRC homology) domains; N-term SH3 and SH2 - SH1 (tyrosine kinase) - DNA binding motif - actin binding domain C-term; widely expressed; localisation is mainly nuclear; inhibits cell growth.

**BCR**

**Location**

22q11

**DNA/RNA**

Various splicings.

**Protein**

Main form: 160 kDa; N-term Serine-Treonine kinase domain, SH2 binding, and C-term domain which functions as a GTPase activating protein for p21rac; widely expressed; cytoplasmic localisation; protein kinase; probable role in signal transduction.

**Result of the chromosomal anomaly**

**Hybrid gene**

**Description**

1- The crucial event lies on der(22), id est 5′ BCR/3′ ABL hybrid gene is pathogenic, while ABL/BCR may or may not be expressed;
2- Breakpoint in ABL is variable over a region of 200 kb, often between the two alternative exons 1b and 1a, sometimes 5′ of 1b, or 3′ of 1a, but always 5′ of exon 2;
3- Breakpoint in BCR is in a narrow region, therefore called M-bcr (for major breakpoint cluster region), a cluster of 5.8 kb, between exons 12 and 16, also called b1 to b5 of M-bcr; most breakpoints being either between b2 and b3, or between b3 and b4.

**Transcript**

8.5 kb mRNA, resulting in a 210 kDa chimeric protein.

**Detection**

RT-PCR for minimal residual disease detection.

**Fusion protein**

**Description**

P210 with the first 902 or 927 amino acids from BCR; BCR/ABL has a cytoplasmic localization, in contrast with ABL, mostly nuclear. It is now clearly established that BCR-ABL is the oncogene responsible for the occurrence of CML. The hybrid protein has an increased protein kinase activity compared to ABL: 3BP1 (binding protein) binds normal ABL on SH3 domain, which prevents SH1 activation; with BCR/ABL, the first (N-terminal) exon of BCR binds to SH2, hiding SH3 which, as a consequence, cannot be bound to 3BP1, thereof, SH1 is activated.

**Oncogenesis**

A- Major molecular pathways activated by BCR-ABL.
    1- BCR/ABL activates RAS signaling through the GRB2 adaptor molecule which interacts specifically with the Y177 of BCR.
    2- PI3-K (phosphatidyl inositol 3′ kinase) pathway is also activated with secondary activation of the AKT/PKB pathway.
    3- Integrity of transcription machinery induced by MYC is necessary for the transforming action of BCR-ABL.
    4- More recently, activation of STAT (Signal transducers and activators of transcription) molecules has been described as a major molecular signaling event induced by BCR-ABL, with activation of essentially STAT5, 1, and 6.
    5- Activation of the molecules of the focal adhesion complex (PAXILLIN, FAK) by BCR-ABL requires the role of the adaptor molecule CRK-L.
    6- BCR-ABL activates negative regulatory molecules such as PTP1B and Abi-1 and their inactivation could be associated with progression into blast crisis.
B- Correlations between molecular pathways and leukemic phenotype observed in primary CML cells or in BCR-ABL-transduced cells are currently limited.
    1- BCR-ABL has anti-apoptotic activity (PI63K/Akt/STAT5).
    2- BCR/ABL induces cell adhesive and migratory abnormalities in vitro in the presence of fibronectin or in transwell assays (Abnormal integrin signaling/FAK/CRK-L/Abnormal response to chemokine SDF-1).
    3- BCR-ABL induces a dose-effect relationship in CML cells with increased BCR-ABL mRNA during progression into blast crisis, with induction of genetic instability.
4- Molecular events associated with blast crisis: P53 mutation, methylation of ABL promoter, telomere shortening, Abl-1 inactivation.

To be noted

Note
1- Blast crisis is sometimes at the first onset of CML, and those cases may be indistinguishable from true ALL or ANLL with t(9;22) and P210 BCR/ABL hybrid;
2- JCML (juvenile chronic myelogenous leukaemia) is not the juvenile form of chronic myelogenous leukaemia: there is no t(9;22) nor BCR/ABL hybrid in JCML, and clinical features (including a worse prognosis) are not similar to those found in CML;
3- so called BCR/ABL negative CML should not be called so!
4- P53 is altered in 1/3 of BC-CML cases.
5- Most recent developments: Evidence of telomere shortening in CML cells during progression into blast crisis.

References


Oda T, Henney C, Hagopian JR, Okuda K, Griffin JD, Druker BJ. Crkl is the major tyrosine-phosphorylated protein in neutrophils from patients with chronic myelogenous leukaemia. J Biol Chem. 1994 Sep 16;269(37):22925-8

This article should be referenced as such: