Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Leukaemia Section

Mini Review

Chronic myelogenous leukaemia (CML)

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Published in Atlas Database: December 1997

Online version is available at: http://AtlasGeneticsOncology.org/Anomalies/CML.html
DOI: 10.4267/2042/32067

Clinics and pathology

Disease

CML is a chronic myeloproliferative syndrome.

Phenotype / cell stem origin

Multipotent (and primitive: CD34+, DR-) progenitor: t(9;22) is found in any myeloid progenitor and in B-lymphocytes progenitors, but, most often, not in the T-cells.

Epidemiology

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

Clinics

Splenomegaly; chronic phase (lasts about 3 yrs) with maintained cell's normal activities, followed by accelerated phase(s)(blasts still < 15%), and blast crisis (BC-CML) with blast cells > 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

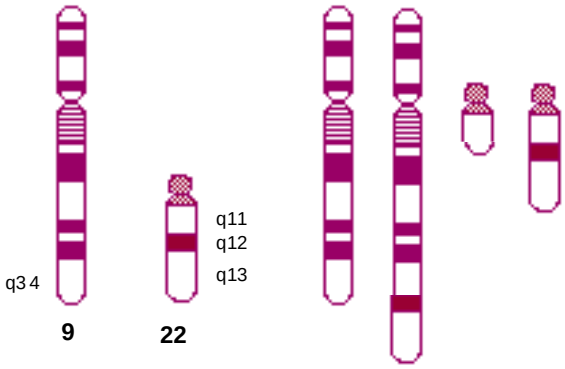
Hyperplastic bone marrow; granulocytes proliferation, with maturation; followed by typical AL cytology (see: t(9;22)(q34;q11) in ALL, t(9;22)(q34;q11) in ANLL).

Treatment

AlphaIFN therapy or bone marrow transplantation (BMT), donor leukocytes infusions.

Prognosis

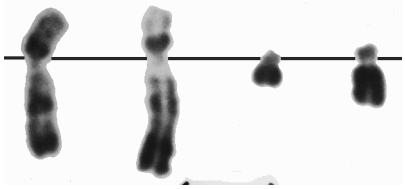
Median survival: 4 yrs with conventional therapy (hydroxyurea, busulfan), 6 yrs with alphaIFN therapy; bone marrow transplantation may cure the patient; otherwise, the best treatment to date associates interferon alpha, hydroxyurea and cytarabine.



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, 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.

Variants

t(9;22;V) and apparent t(V;22) or t(9;V), where V is a variable 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-Threonine 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.

Results 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 protocol

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, hidding SH3 which, as a consequence, cannot be bound to 3BP1; thereof, SH1 is activated.

Oncogenesis

1. Proliferation is induced: there is activation by BCR/ABL of Ras signal transduction pathway via it's linkage to son-of-sevenless (SOS), a Ras activator; PI3-K (phosphatidyl inositol 3' kinase) pathway is also activated; MYC as well;
2. BCR/ABL inhibits apoptosis;
3. BCR/ABL provokes cell adhesive abnormalities: impaired adherence to bone marrow stroma cells, which allows unregulated proliferation of leukaemic progenitors.

To be noted

1. Blast crisis is sometimes at the first onset of CML, and those cases may be undistinguishable 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.

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This article should be referenced as such:

Huret JL. Chronic myelogenous leukaemia (CML). Atlas Genet Cytogenet Oncol Haematol.1997;1(2):89-91.