Chronic myelogenous leukaemia (CML)

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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: 10/10⁶ (from 1/10⁶ in childhood to 30/10⁶ 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 10⁹/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, 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, hinding 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.

References


This article should be referenced as such: