Leukaemia Section
Mini Review

**t(9;22)(q34;q11) in CML**

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**Identity**

**Note:** Although the same hybrid genes issued from ABL and BCR are the hallmark of the t(9;22) translocation, this translocation may be seen in the following diseases: CML, ANLL, and ALL, and will therefore be described in the 3 different situations: t(9;22)(q34;q11) in CML, t(9;22)(q34;q11) in ALL, t(9;22)(q34;q11) in ANLL.

t(9;22)(q34;q11) in CML is herein described.

**Clinics and pathology**

**Disease**

CML: 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, as already noted.

**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)/ANLL, and t(9;22)(q34;q11)/ALL).

**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**
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; this may have a carcinogenetic role. 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**
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 (phosphatidylinositol 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 leukemic progenitors.
To be noted

Specific comments on this translocation:

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 leukemia: 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: