

# Leukaemia Section

## Mini Review

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

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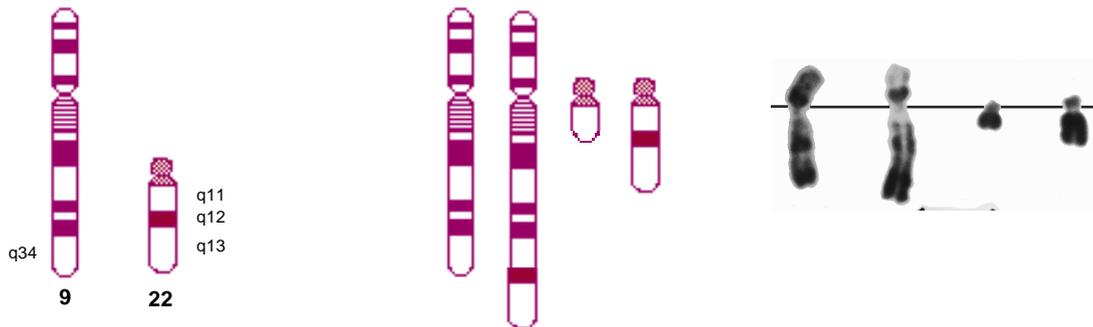
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## Identity

**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<sup>6</sup> (from 1/10<sup>6</sup> in childhood to 30/10<sup>6</sup> 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<sup>9</sup>/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 protocole**

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 its 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 leukaemic 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 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

- Sokal JE, Gomez GA, Baccarani M, Tura S, Clarkson BD, Cervantes F, Rozman C, Carbonell F, Anger B, Heimpel H, et al. Prognostic significance of additional cytogenetic abnormalities at diagnosis of Philadelphia chromosome-positive chronic granulocytic leukemia. *Blood* 1988;72:294-298.
- Huret JL. Complex translocations, simple variant translocations and Ph-negative cases in chronic myelogenous leukemia. *Hum Genet* 1990;85:565-568. (Review).
- Heisterkamp N, Groffen J. Molecular insights into the Philadelphia translocation. *Hematol Pathol* 1991;5:1-10. (Review).
- Kurzrock R, Talpaz M. The molecular pathology of chronic myelogenous leukemia. *Br J Haematol* 1991;79 Suppl 1:34-37. (Review).
- Martiat P, Michaux JL, Rodhain J. Philadelphia-negative (Ph-) chronic myeloid leukemia (CML): comparison with Ph+ CML and chronic myelomonocytic leukemia. The Groupe Français de Cytogénétique Hématologique. *Blood* 1991;78:205-112.
- Gale RP, Grosveld G, Canaani E, Goldman JM. Chronic myelogenous leukemia: biology and therapy. *Leukemia* 1993;7:653-658.
- Enright H, McGlave PB. Chronic myelogenous leukemia. *Curr Opin Hematol* 1995;2:293-299. (Review).
- Gotoh A, Broxmeyer HE. The function of BCR/ABL and related proto-oncogenes. *Curr Opin Hematol* 1997;4:3-11. (Review).
- Guilhot F, Chastang C, Michallet M, Guerci A, Harousseau JL, Maloisel F, Bouabdallah R, Guyotat D, Cheron N, Nicolini F, Abgrall JF, Tanzer J. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. French Chronic Myeloid Leukemia Study Group. *N Engl J Med* 1997;337:223-229.

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