Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Educational Items Section

Malignant blood diseases

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Published in Atlas Database: June 2000

Online updated version : http://AtlasGeneticsOncology.org/Educ/Hempat_e.html
DOI: 10.4267/2042/37659

I- Introduction

Malignant blood diseases may be classified:

- According to the clinical course:
  - chronic leukemias
  - acute leukemias
- According to the lineage:
  - lymphoid lineage: B or T
  - myeloid lineage:
    - myeloproliferative syndromes: quantitative anomalies
    - myelodysplastic syndromes: qualitative anomalies
    - acute myeloid leukemias (or acute non lymphoblastic leukemias)
- According to the primary site:
  - leukemia: originates in the bone marrow; flows into the peripheral blood
  - lymphoma: originates in the lymph nodes; invades bone marrow and blood

The cell Morphology (according to the FAB (French-American-British) classification of leukemias), the Immunophenotype and the Cytogenetic findings (MIC) allow a specific classification.

II- Myeloproliferative syndromes

Myeloproliferations: quantitatives anomalies of the myeloid lineage.

II-1. Chronic myeloid leukemia (CML)

- malignant monoclonal process involving a pluripotent hematopoietic progenitor (therefore, most of the lineages are implicated)
- splenomegaly, high leukocyte count, basophilia, immature cells in the peripheral blood, low leucocyte alkaline phosphatase, bone marrow expansion with increased neutrophil lineage
- prognosis: chronic phase, followed by blast crises, ending in an acute transformation; median survival used to be of 4 yrs before the new treatments

Chromosome anomalies:

- **t(9;22)(q34;q11)**
- chromosome 22 appears shorter and was called Philadelphia chromosome (noted Ph)
- translocates (part of) an oncogene, ABL, sitting usually in 9q34, next to (part of) another oncogene, BCR (breakpoint cluster region), in 22q11 --> production of a hybrid gene 5' BCR-3'ABL
- the normal ABL is transcribed into a m-RNA of 6 to 7 kbases, which produces a protein (tyrosine kinase) of 145 kDalton
- the hybrid gene BCR-ABL, result of the translocation t(9;22), is transcribed into a m-RNA of 8.5 kb, which produces a protein of 210 kDa with: 1) an increased protein kinase activity 2) an increased half-life, as compared to normal ABL
- In a percentage of cases, there is a variant translocation, also implicating a third chromosome (e.g. t(1;9;22)); the implication of chromosome 9 or chromosome 22 may even be hidden (e.g. t(12;22); at times, finally, the karyotype seems normal ("Ph-CML"); however, the gene hybride BCR-ABL is always present (otherwise, it is NOT a CML!)
- therefore the translocation t(9;22) is the specific anomaly found in CML however, this anomaly is not pathognomonic, as it may also be found in ALL or in ANLL
- additionnal anomalies : most often found at the time of the blast crisis, they may also be present at diagnosis; mainly: +Ph, and/or +8, and/or (17q), and/or +19, and/or -7; clonal evolution

II- 2. Other myeloproliferative syndromes

• **Polycytemia vera (PV)** : red cell lineage mainly; median survival: 10 to 15 yrs

• **Idiopathic myelofibrosis** (or agnogenic myeloid metaplasia) : splenic metaplasia with progressive myelofibrosis ; survival is very variable (3 to 15 yrs)

Chromosome anomalies:

- rare at diagnosis: del(20q), or +8, or +9, or del (13q), or partial trisomy for 1q
- frequent during acute transformation: anomalies are the one found in usual ANLL or in secondary leukemias (see below)

• **Essential thrombocythemia (ET)**: megakaryocytic lineage mainly; survival = 10 yrs; chromosome anomalies are rare

III- Myelodysplastic syndromes (MDS)

Dysmyelopoiesis: qualitative anomalies of the myeloid lineage

Classified according to the FAB:

- refractory anemia without excess of blasts (RA)
- refractory anemia with excess of blasts (RAEB)
- refractory anemia with ringed sideroblasts (RARS)
- chronic myelomonocytic leukemia (CMML)
- Aside : secondary myelodysplasias (see secondary acute leukemias)

Chromosome anomalies :

- del(5q) (or -5, of identical signification)
- del(7q) (or -7, equivalent)
- +8
- various structural rearrangements of: 11q, 12p, or chromosome 3

IV- Acute non lymphoblastic leucemias (ANLL)

or acute myeloid leukemias (AML), the term myeloid being a bit confusing

• massive proliferation of myeloid precursors;
• the chromosome anomaly bears a prognostic value

Classified according to the FAB:

- M1 : myeloblastic without maturation
- M2 : myeloblastic with maturation
- M3 : promyelocytic
- M4 : myelomonocytic
- M5 : monocytic
- M6 : erythroleukemia
- M7 : megakaryoblastic

Chromosome anomalies, main entities:

• **t(8;21)(q22;q22)** : mainly in M2-ANLL; genes ETO and AML1

• **t(15;17)(q25;q21)** : (quasi) pathognomonic of M3-ANLL; genes PML and RARA fair prognosis if DIC is prevented and with the new treatments (differenciation therapy) (and also as compared with other ANLL)

• **inv(16)(p13q22)**: pathognomonic of M4-ANLL with eosinophilia; genes MYH11 and CBFb good prognosis: median survival = 5 yrs

• t(9;22)(q34;q11): rare in ANLL; most often in M1 or M2 ANLL; BCR-ABL as in CML in half cases (protein bcr-abl of 210 kDa, called P210), break at a different

locus in the other half cases with a m-RNA of 7 to 7.5 kb, and production of a bcr-abl protein of 190 kDa (named P190) with even a higher transforming ability than P210); very poor prognosis

- **t(6;9(p23;q34)** : low specificity; often associated with basophilia; genes DEK and CAN; poor prognosis
- 3q21 rearrangements : associated with thrombocytosis; very poor prognosis
- 11q23 rearrangements (M4, M5, biphenotypic acute leukemias) of which is the t(9;11)(p22;q23)
- Other: del (20q) , +8, del (5q), del (7q), 12p rearrangements.

V- Secondary acute leukemias

- induced leukemias: treatment related (or "therapy related") leukemia (after chemo and/or radiotherapy for a prior cancer), or leukemia after professional exposure to carcinogenetic (genotoxic) chemicals or physical agents
- very poor prognosis

Chromosome anomalies : frequent, often complex:

- multiple monosomies (hypoploidy)
- **del(5q) or -5**
- del(7q) or -7
- rearrangements 6p, 12p, 17p, 11q23...

VI- Acute lymphoblastic leukemias (ALL)

- heavy proliferation of B or T lymphoid precursors,
- the immunophenotyping (CD, Ig) allows the recognition of the lineage involved in the malignant process, and the degree of maturation of the malignant cell
- the morphology differenciates ALL1 and 2 on one hand, and ALL3 with large Burkitt-type cells on the other hand
- --> MIC classification (Morphology, Immunophenotype, Cytogenetics) allows to define entities with given prognoses
- ALL often occur in childhood

Chromosome anomalies, main entities:

- **t(4;11)(q21;q23)** : immature (CD19+) B-cell; occurs often in childhood, especially very early (congenital leukemia, before 1 yr); very poor prognosis (median survival below 1 yr), the treatment being a bone marrow graft; genes MLL in 11q23 and AF4 in 4q21
- other 11q23 ; MLL and a shared clinical profile
- **t(9;22)(q34;q11)** : B-cell; very poor prognosis; at the molecular level: ABL and BCR ; P210 in half cases, P190 in the other half, as is in ANLL with t(9;22)
- **t(12;21)(p12;q22)** : CD10+ B ALL in childhood; genes ETV6 and AML1
- t(8;14)(q24;q32) and variants t(2;8)(p12;q24) and t(8;22)(q24;q11): t(8;14) being the most frequent; quasi pathognomonic of L3-ALL and Burkitt lymphoma (mature B malignant cell); the prognosis was poor until recently, where new treatments are accompanied with better outcome; MYC in 8q24; immunoglobulin heavy-chains (IgH) in 14q32, or light-chains K (Ig K) in 2p12 and L (IgL) in 22q11; these translocations set the oncogene under the regulation of immunoglobulin transcription stimulating sequences (active in the B-lineage), leading to overexpression
- t(11;14)(p13;q11), t(8;14)(q24;q11) and t(10;14)(q24;q11) : T-cell leukemia; T-cell receptor (TCR D et A) belonging to the immunoglobulin superfamilly in 14q11; RBTN2 in 11p13, HOX11 in 10q24, and, obviously, MYC in 8q24; comparable to the above, with here an oncogene under the regulation of the T-cell receptor transcription stimulating sequences (active in the T-lineage), leading to overexpression
- del(6q), 9p rearrangements, 12p rearrangements, quasi-haploidy, hyperploidy (hyperploidy _ 50 ; hyperploidy > 50, they are of good prognosis), are not rare ALL

VII- Non hodgkin's lymphomas

- classified into numerous categories (see non Hodgkin lymphomas classification according to the cell and tissue morphology, and correlated with the prognosis (low to high grades)
- chronic lymphoid leukemia is considered as a leukemia by the haematologists and as a low grade lymphoma by the pathologists
- **Chronic lymphoid leukemia (CLL):** often a very slow process (10-15 yrs), at times very fast

Chromosome anomalies:

- +12, 14q32 rearrangements , del(6q) , 13q rearrangements, del(11q), +3, +18 , non identifiable markers; often as associated anomalies

- **Non Hodgkin's lymphomas (NHL)**

chromosome anomalies:

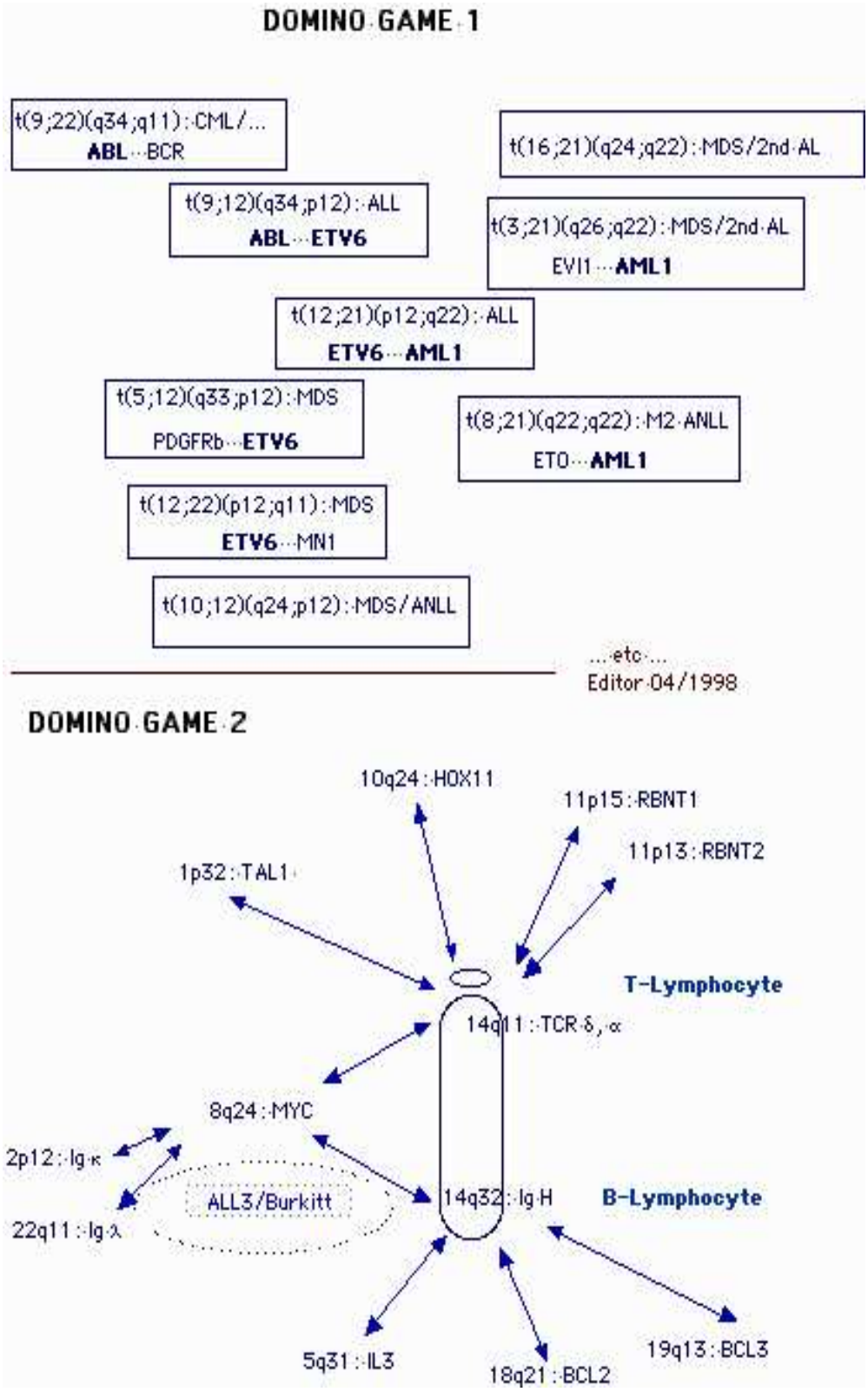
- **t(14;18)(q32;q21)** : typically, found in small cleaved B-cell lymphomas; BCL2 (B cell lymphoma 2) in 18q21, a gene of the BCL2/BAX familly, implicated in the abrogation/induction of apoptosis ("programmed cell death"), immunoglobulin heavy-chain (IgH) in 14q32; BCL2 (protein of the inner membrane of the mitochondria), in case of a translocation t(14;18), is set under the regulation of immunoglobulin transcription stimulating sequences (active in the B-lineage), and overexpressed (as above)
- other 14q32 rearrangements: of which is the t(11;14)(q13;q32) often seen in mantle cell lymphomas
- 14q11 rearrangements: T-cell lymphomas; TCR A et D (T-cell receptor) in 14q11, and, at the breakpoint on the partner chromosome, an

oncogene, overexpressed when put under the regulation of the T-cell receptor transcription stimulating sequences (active in the T-lineage)
- various rearrangements, unrecognizable markers, multiple and complex anomalies are not rares in NHL

VIII- Main chromosome anomalies in malignant blood diseases

1	chrom 1 rearrangements	various
2	t(2;8)(p12;q24)	L3-ALL and Burkitt
4	t(4;11)(q21;q23)	ALL
5	del(5q) or -5	MDS, ANLL, Second Leuk.
6	del(6q)	ALL, CLL, NHL
7	del(7q) or -7	MDS, ANLL, Second Leuk.
8	t(2;8)	see chromosome 2
	t(8;14)(q24;q32)	L3-ALL and Burkitt
	(8;14)(q24;q11)	T-ALL
	t(8;21)(q22;q22)	M2-ANLL
	+8	various, myeloid
9	t(9;22)(q34;q11)	CML, ANLL, ALL
	del(9p)	ALL
	+9	various
11	t(4;11)	see chromosome 4
	t(11;14)(p13;q11)	T-ALL
	t(11;14)(q13;q32)	NHL
	del(11q)	MDS, ANLL, CLL
12	+12	CLL, NHL
	t(12;21)(p12;q22)	ALL
13	del(13q)	various
14	t(8;14)	see chromosome 8
	(11;14)	see chromosome 11
	t(14;18)(q32;q21)	NHL
	inv(14)(q11q32)	T-lymphocyte
15	t(15;17)(q22;q12)	M3-ANLL
16	16q22 rearrangement	M4-ANLL
17	t(15;17)	see chromosome 15
	i(17q)	CML
18	t(14;18)	see chromosome 14
20	del(20q)	myeloid
21	t(8;21)	see chromosome 8
	t(12;21)	see chromosome 12
22	t(8;22)	see chromosome 8
	t(9;22)	see chromosome 9
Other	hypoploidy	Second Leuk., ALL
	hyperploidy	Second Leuk., ALL, NHL
	marker	Second Leuk., CLL, NHL

IX- Domino game



This article should be referenced as such:

Huret JL. Malignant blood diseases. Atlas Genet Cytogenet Oncol Haematol. 2000; 4(3):174-178.