

Malignant Blood Diseases

Introduction

Myeloproliferative syndromes

Myelodysplastic syndromes (MDS)

Acute Non Lymphoblastic Leukemias (ANLL)

Secondary acute leukemias

Acute Lymphoblastic Leukemias (ALL)

Non Hodgkin's Lymphomas

Main chromosome anomalies in malignant blood diseases

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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.

MYELOPROLIFERATIVE SYNDROMES

Myeloproliferations : quantitatives anomalies of the myeloid lineage.

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.
- Additional 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

Other myeloproliferative syndromes

[Polycythemia 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

MYELOYDYSPLASTIC 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 sideroblástica \(RARS\)](#)
- [chronic myelomonocytic leukemia \(CMM L\)](#)
- 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
-

ACUTE NON LYMPHOBLASTIC LEUKEMIAS ([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 (differentiation 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](#).

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](#)...
-

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 differentiates 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 ([IgK](#)) 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\(8;14\)\(q24;q11\)](#) y [t\(10;14\)\(q24;q11\)](#) : T-cell leukemia; T-cell receptor ([TCR D](#) and [A](#)) belonging to the immunoglobulin superfamily 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.

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 family, 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.

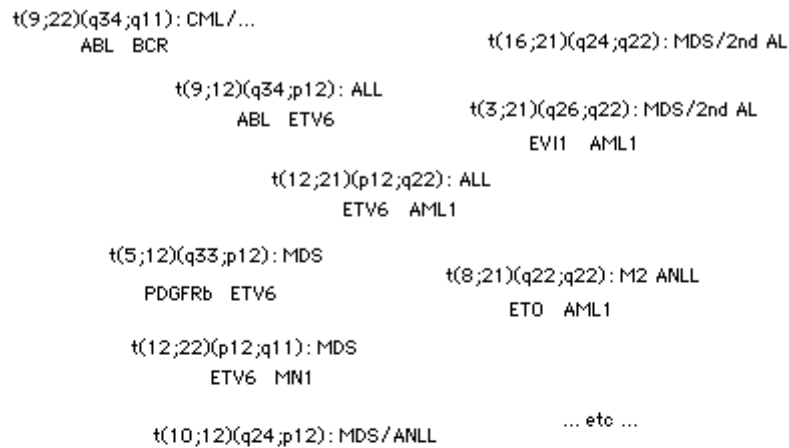
Main chromosome anomalies in malignant blood diseases

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) o -5	MDS, ANLL, Second Leuk.
6	del(6q)	ALL, CLL, NHL
7	del(7q) o -7	MDS, ANLL, Second Leuk.
8	t(2;8)	see chromosome 2
	t(8;14)(q24;q32)	L3-ALL and Burkitt
	t(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

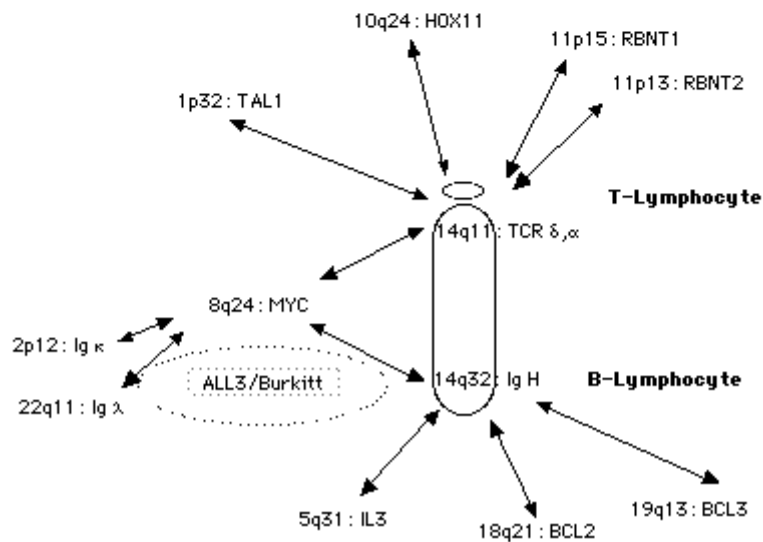
16	16q22 rearrangement	M4-ANLL
17	t(15;17)	see chromosome 15
	i(17q)	CML
18	t(14;18)	see chromosome 14
20	del(20q)	myeloid
21	t(8;21)	see chromosome 8
	t(12;21)	see chromosome 12
22	t(8;22)	see chromosome 8
	t(9;22)	see chromosome 9
Other	hypoploidy	Second Leuk., ALL
	hyperploidy	Second Leuk., ALL , NHL
	marker	Second Leuk., CLL, NHL

For a more complete list, see [LIST of CYTOGENETIC / CLINICAL ENTITIES in HAEMATOLOGY](#)

DOMINO GAME 1



DOMINO GAME 2



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