HEMATOLOGY

LYMPHOID SERIES DISORDERS

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White cell counts

- Low white cell counts are seen with viral infection, steroid use, and chronic marijuana use.
- An increased absolute monocyte count is consistent with myelodysplasia.
- Elevation of the monocyte count above 7% indicates an immune defense reaction. An elevated absolute monocyte cell count accompanied by a drop in absolute cell counts in other series suggests monocytic leukemia.
- An infant with a low white count and 100% lymphocytosis with morphologically normal lymphocytes probably has an infection with B. pertussis.

White cell counts

- Chickenpox, measles, brucellosis associated with lymphocytosis and normal white cell counts.
- Hyperthyroidism and Addison disease
- Constitutional relative lymphocytosis can reach up to 60% and occurs without apparent reason (mostly in asthenic teenagers).
- Absolute granulocytopenias with relative Lymphocytosis
- Chronic lymphocytic leukemia (CLL), which is always accompanied by absolute and relative lymphocytosis, usually with high cell counts.

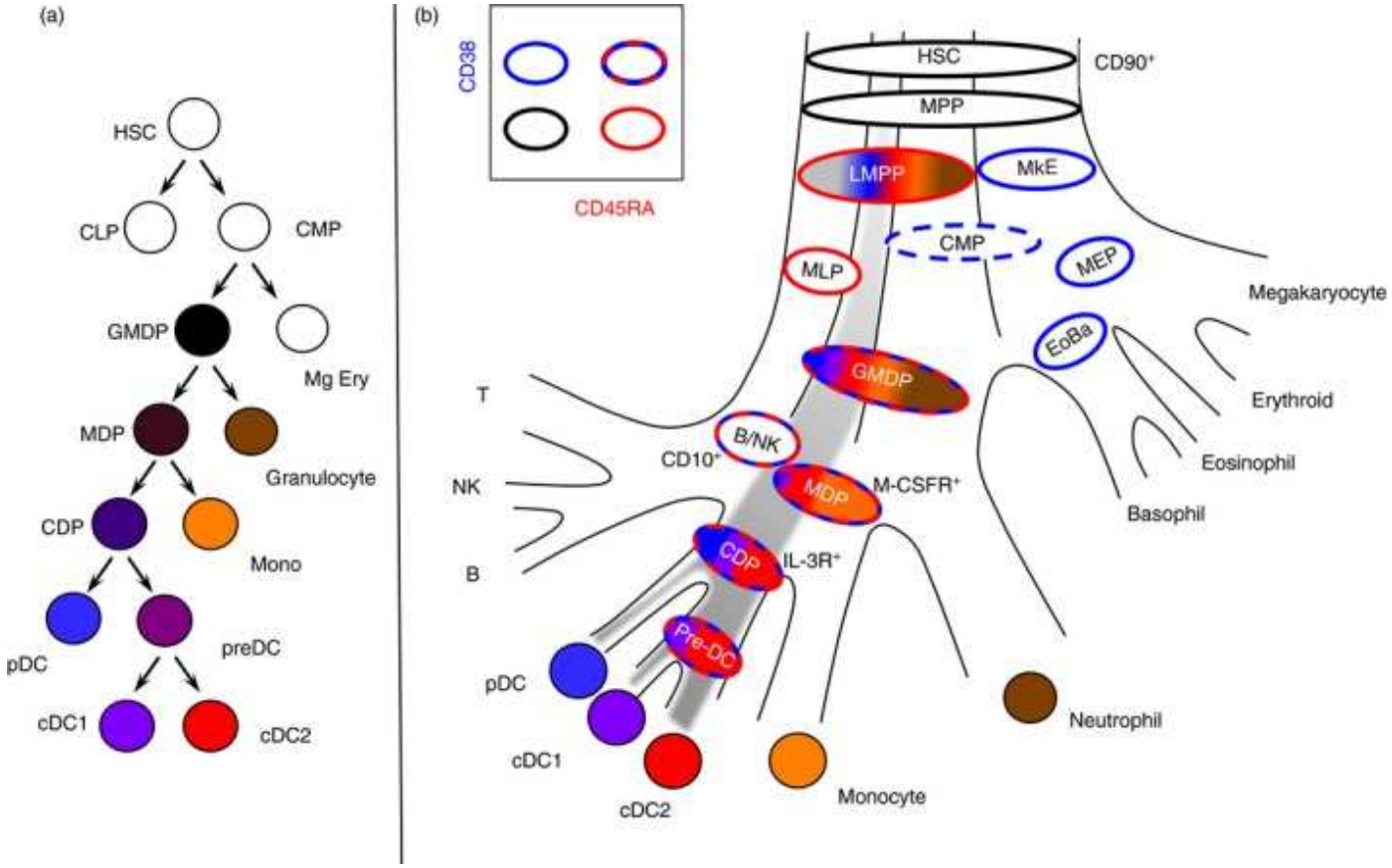
White cell morphology

- Transformed, “stimulated” lymphocytes may be seen with toxoplasmosis (normal white cell counts), rubella (normal or low white cell counts), and hepatitis (normal or low white cell counts).
- The most extreme lymphocyte transformation is observed in mononucleosis (Epstein–Barr virus (EBV) or cytomegalovirus (CMV) infection)

White cell life spans

- B-lymphocyte (circulating) 10-14 days
- T-cell (in contact with antigen) 15 weeks
- Plasma cell (if no B-lymphocyte memory cell present) >1 year

Classic and revised models of hematopoiesis



Common myeloid progenitors are mixtures of mega-erythroid and myeloid precursors and the most significant early partitioning of cell fate occurs when megakaryocyte and erythroid potentials separate from lympho-myeloid potentials.

Doi: 10.1111/imm.12888

Maturation of blood cells

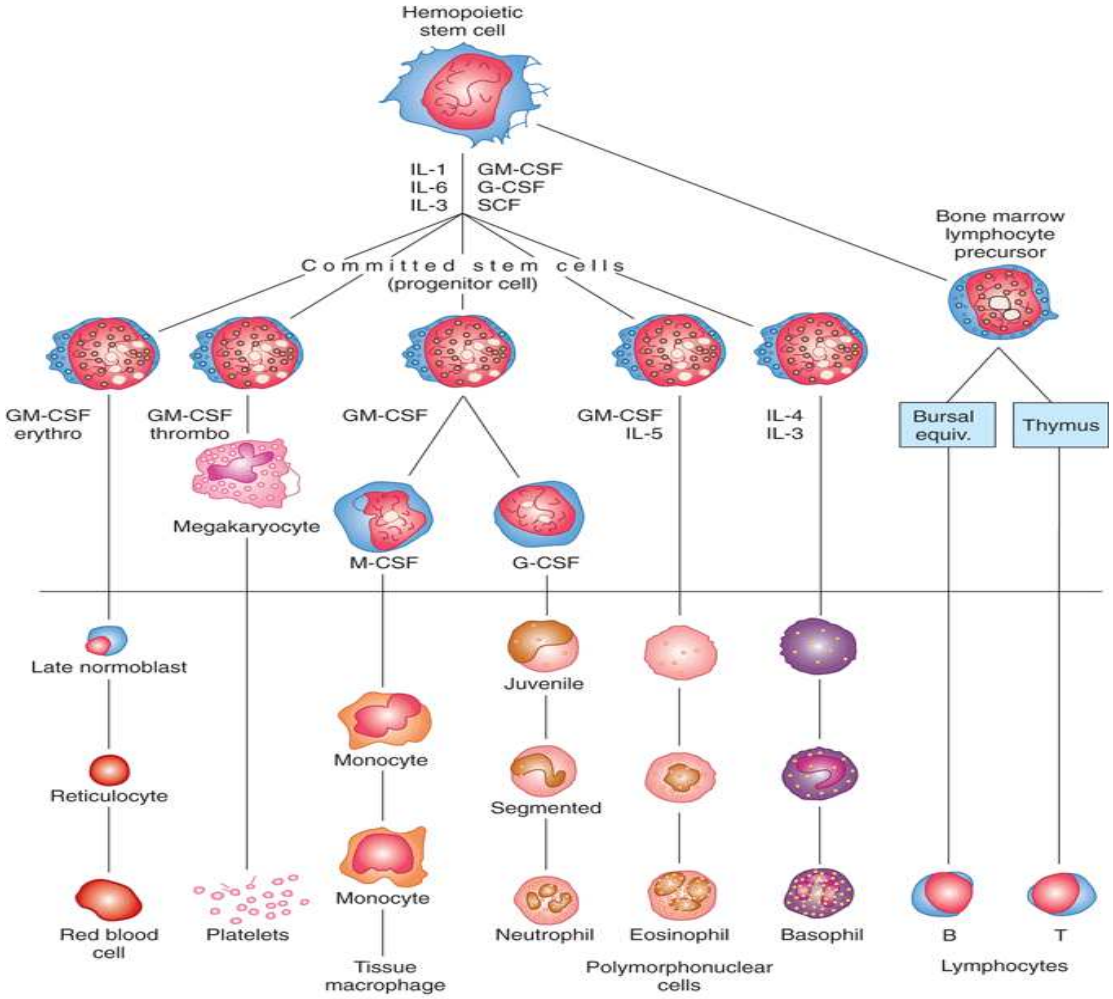
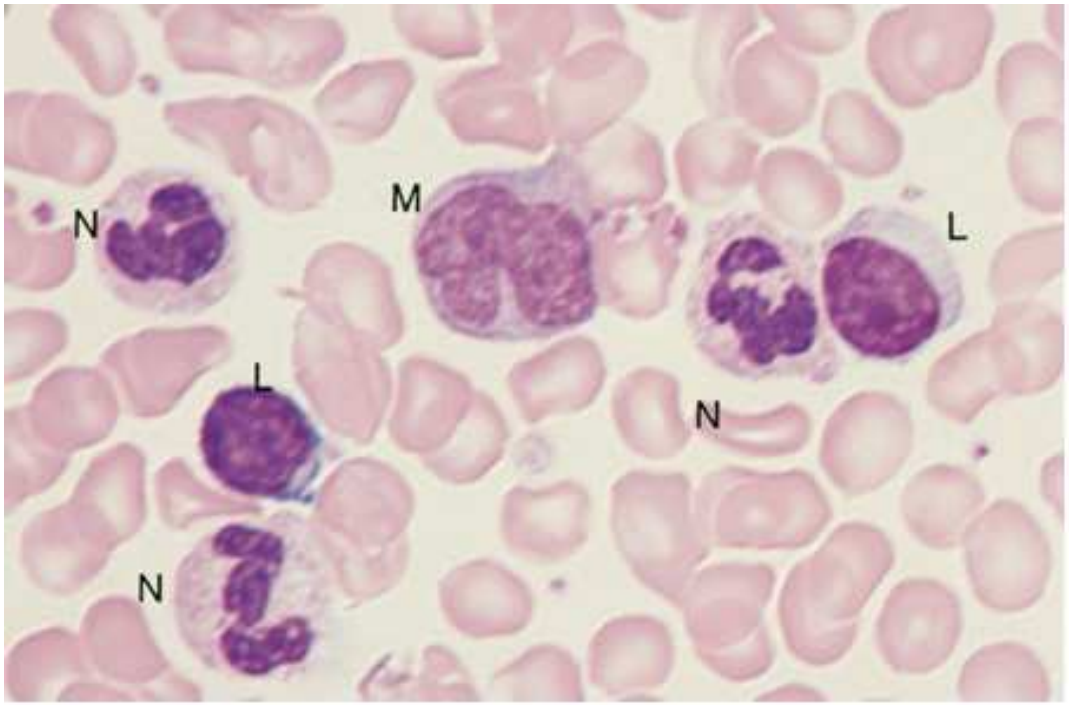


Fig. 32-3 Accessed 02/01/2010

Mononuclear cells

- Small lymphocytes have a small dark nucleus and scant cytoplasm. They are the lymphocytes most commonly found in the peripheral blood. They are the size of a red cell.
- Large granular lymphocytes contain blue granules in a light blue cytoplasm. These are generally few in number.
- Monocytes are the largest white blood cells. The nucleus can take on a variety of shapes but usually appears to be ovoid, folded, irregular in outline. The nuclear chromatin is fine. The cytoplasm is gray.

Mononuclear cells



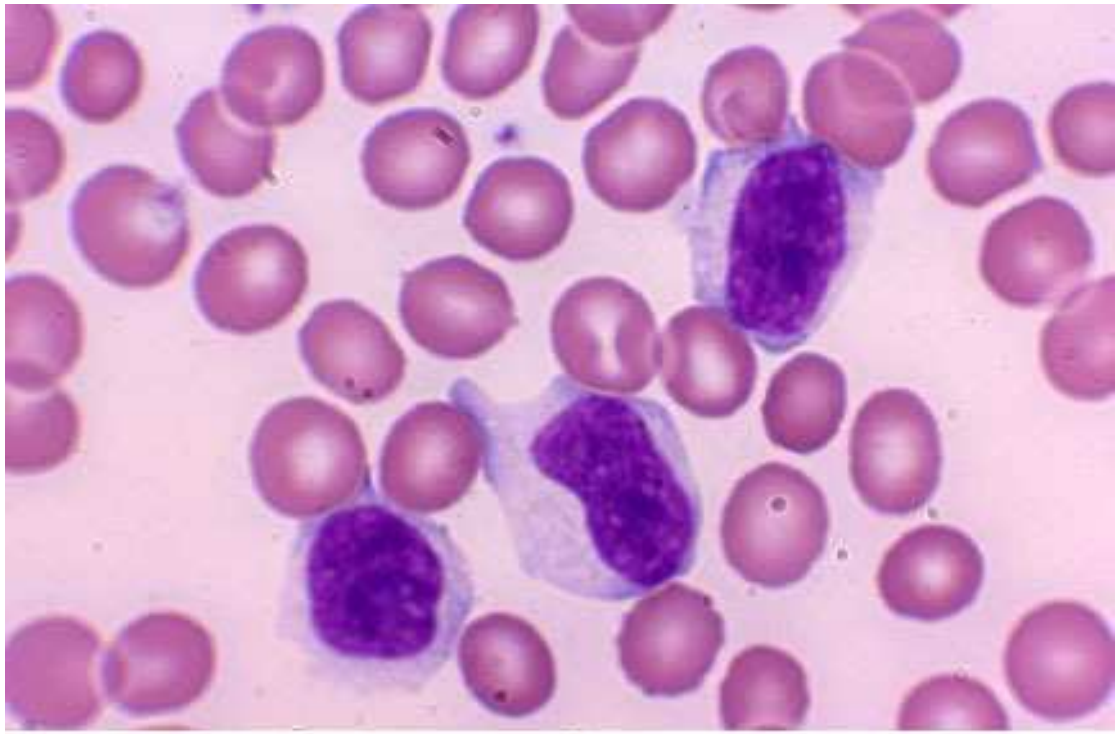
L, lymphocyte**; M,** monocyte**; N,** neutrophil

Fig. e11-27 Accessed 02/01/2010

Mononuclear cells

- Reactive lymphocytes are found in the presence of viral infections. The lymphocytes are the size of a neutrophil, have abundant cytoplasm and a less condensed nuclear chromatin.
- Smudge cells and are rare in the absence of chronic lymphoid leukemia. These are small lymphocytes ruptured in making the blood smear, leaving a smudge of nuclear material without a surrounding cytoplasm or cell membrane.

Atypical lymphocytes



Source: Lichtman MA, Shafer MS, Felgar RE, Wang N:
Lichtman's Atlas of Hematology: http://www.accessmedicine.com

Cytoplasmic periphery conforms to red cell outlines. Nuclear shape not a strict circle but elongated or irregular.

Fig. II.G.9
Accessed 02/01/2010

Clues from examination of the bone marrow

- Bone marrow cytology allows a quantitative assessment only in relative terms.
- In adults, normal marrow cellularity is 35–40%.
- The important ratio of red precursor cells to white cells is 1 : 2 for men and 1 : 3 for women.

Immunophenotype as basis for EGIL classification: ALL subtypes include B and T cell lineages and different maturation stages

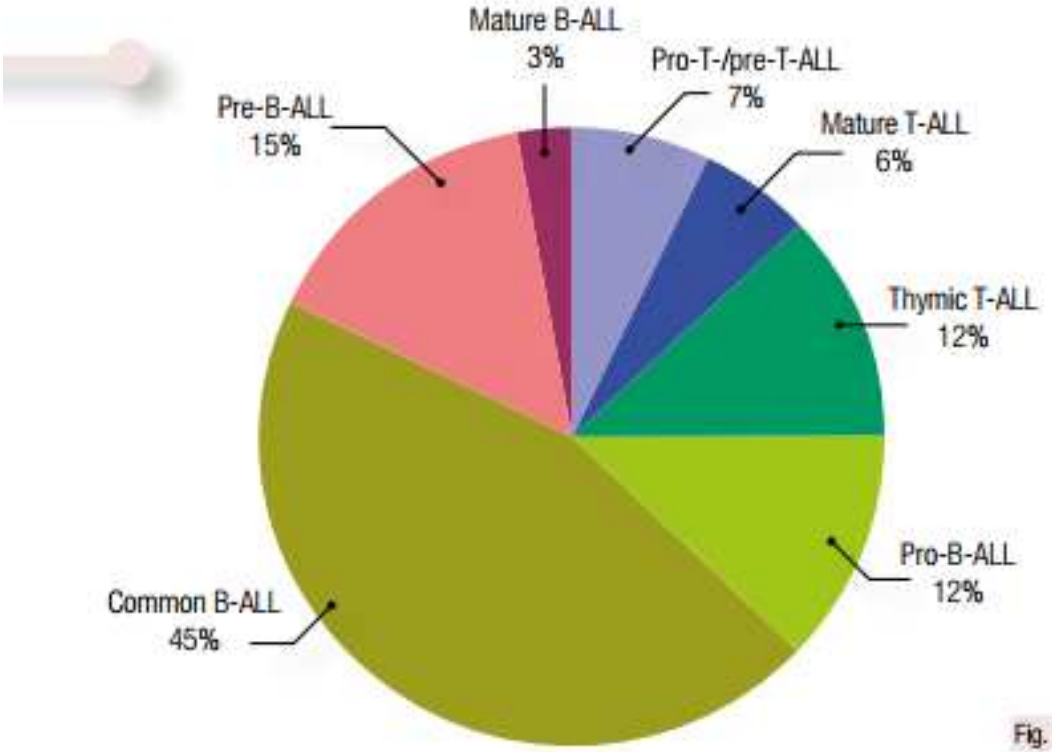


Fig. 1.13

ALL, Acute lymphoblastic leukaemia; EGIL, European Group for the Immunological Characterization of Leukaemias.

The FAB classification for ALL is no longer in use.

The IPSS-R score uses diagnostic parameters at initial presentation to define the patient's risk for progression and death

Subgroup	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	–	Good	–	Intermediate	Poor	Very poor
BM blast, %	≤2	–	>2–<5	–	5–10	>10	
Haemoglobin	≥10	–	8–<10	<8	–	–	–
Platelets	≥100	50–100	<50	–	–	–	–
Neutrophils	≥0.8	<0.8	–	–	–	–	–

Risk category: very low ≤1.5, low >1.5–3, intermediate >3–4.5, high >4.5–6, very high >6
BM, Bone marrow; IPSS-R, Revised International Prognostic Scoring System.

Fig. 1.15

Table 13-6 Summary of Major Types of Lymphoid Leukemias and Non-Hodgkin Lymphomas

Diagnosis	Cell of Origin	Genotype	Salient Clinical Features
Neoplasms of Immature B and T Cells			
B-cell acute lymphoblastic leukemia/lymphoma*	Bone marrow precursor B cell	Diverse chromosomal translocations; t(12;21) involving *RUNX1* and *ETV6* present in 25%	Predominantly children; symptoms relating to marrow replacement and pancytopenia; aggressive
T-cell acute lymphoblastic leukemia/lymphoma	Precursor T cell (often of thymic origin)	Diverse chromosomal translocations, *NOTCH1* mutations (50%-70%)	Predominantly adolescent males; thymic masses and variable bone marrow involvement; aggressive
Neoplasms of Mature B Cells			
Burkitt lymphoma*	Germinal-center B cell	Translocations involving *MYC* and Ig loci, usually t(8;14); subset EBV-associated	Adolescents or young adults with extranodal masses; uncommonly presents as "leukemia"; aggressive
Diffuse large B-cell lymphoma†	Germinal-center or postgerminal center B cell	Diverse chromosomal rearrangements, most often of *BCL6* (30%), *BCL2* (10%), or *MYC* (5%)	All ages, but most common in older adults; often appears as a rapidly growing mass; 30% extranodal; aggressive
Extranodal marginal zone lymphoma	Memory B cell	t(11;18), t(1;14), and t(14;18) creating *MALT1-IAP2*, *BCL10-IgH*, and *MALT1-IgH* fusion genes, respectively	Arises at extranodal sites in adults with chronic inflammatory diseases; may remain localized; indolent
Follicular lymphoma†	Germinal-center B cell	t(14;18) creating *BCL2-IgH* fusion gene	Older adults with generalized lymphadenopathy and marrow involvement; indolent
Hairy cell leukemia	Memory B cell	Activating *BRAF* mutations	Older males with pancytopenia and splenomegaly; indolent
Mantle cell lymphoma	Naive B cell	t(11;14) creating *CyclinD1-IgH* fusion gene	Older males with disseminated disease; moderately aggressive
Multiple myeloma/solitary plasmacytoma†	Post-germinal-center bone marrow homing plasma cell	Diverse rearrangements involving *IgH*; 13q deletions	Myeloma: older adults with lytic bone lesions, pathologic fractures, hypercalcemia, and renal failure; moderately aggressive Plasmacytoma: isolated plasma cell masses in bone or soft tissue; indolent
Small lymphocytic lymphoma/chronic lymphocytic leukemia	Naive B cell or memory B cell	Trisomy 12, deletions of 11q, 13q, and 17p	Older adults with bone marrow, lymph node, spleen, and liver disease; autoimmune hemolysis and thrombocytopenia in a minority; indolent
Neoplasms of Mature T Cells or NK Cells			
Adult T-cell leukemia/lymphoma	Helper T cell	HTLV-1 provirus present in tumor cells	Adults with cutaneous lesions, marrow involvement, and hypercalcemia; occurs mainly in Japan, West Africa, and the Caribbean; aggressive
Peripheral T-cell lymphoma, unspecified	Helper or cytotoxic T cell	No specific chromosomal abnormality	Mainly older adults; usually presents with lymphadenopathy; aggressive
Anaplastic large-cell lymphoma	Cytotoxic T cell	Rearrangements of *ALK* (anaplastic large cell lymphoma kinase) in a subset	Children and young adults, usually with lymph node and soft-tissue disease; aggressive
Extranodal NK/T-cell lymphoma	NK-cell (common) or cytotoxic T cell (rare)	EBV-associated; no specific chromosomal abnormality	Adults with destructive extranodal masses, most commonly sinonasal; aggressive
Mycosis fungoides/Sézary syndrome	Helper T cell	No specific chromosomal abnormality	Adult patients with cutaneous patches, plaques, nodules, or generalized erythema; indolent
Large granular lymphocytic leukemia	Two types: cytotoxic T cell and NK cell	Point mutations in *STAT3*	Adult patients with splenomegaly, neutropenia, and anemia, sometimes, accompanied by autoimmune disease

*Most common tumors in children
†Most common tumors in adults.
EBV, Epstein-Barr virus; *HIV*, human immunodeficiency virus; *Ig*, immunoglobulin; *NK*, natural killer.

Leukemia

- Acute leukemia represents a very aggressive, malignant transformation of an early hematologic precursor arrested in an immature, blast form. It no longer has the ability to undergo maturation but may proliferate.
- Chronic leukemia is characterized by resistance to apoptosis and by accumulation of nonfunctional cells.
- Accumulation of cells in the marrow results in progressive hematopoietic failure, with associated infection, anemia, and thrombocytopenia.

Leukemia risks

- Prior radiation
- Down syndrome
- Bloom syndrome
- Fanconi syndrome
- Wiscott-Aldrich syndrome
- Ataxia Telangiectasia

	T-Lineage	B-Precursor	Mature B
Bleeding	28%	28%	30%
Infections	22%	29%	37%
Enlarged lymph nodes	77%	40%	61%
Hepatomegaly	45%	41%	56%
Splenomegaly	55%	43%	47%
Mediastinal tumour	62%	1%	5%
CNS involvement	8%	3%	13%
Other organ involvement	15%	4%	32%

CNS, Central nervous system.

Fig. 3.7

Acute leukemia

- Acute lymphoblastic leukemias (ALLs) are neoplasms composed of immature B (pre-B) or T (pre-T) cells
- 85% B-cell
- ALL most common childhood malignancy
- Peaks at the age of 3
- Loss of function of PAX5, E2A, and EBF, or a balanced t(12;21) involving the genes ETV6 and RUNX1

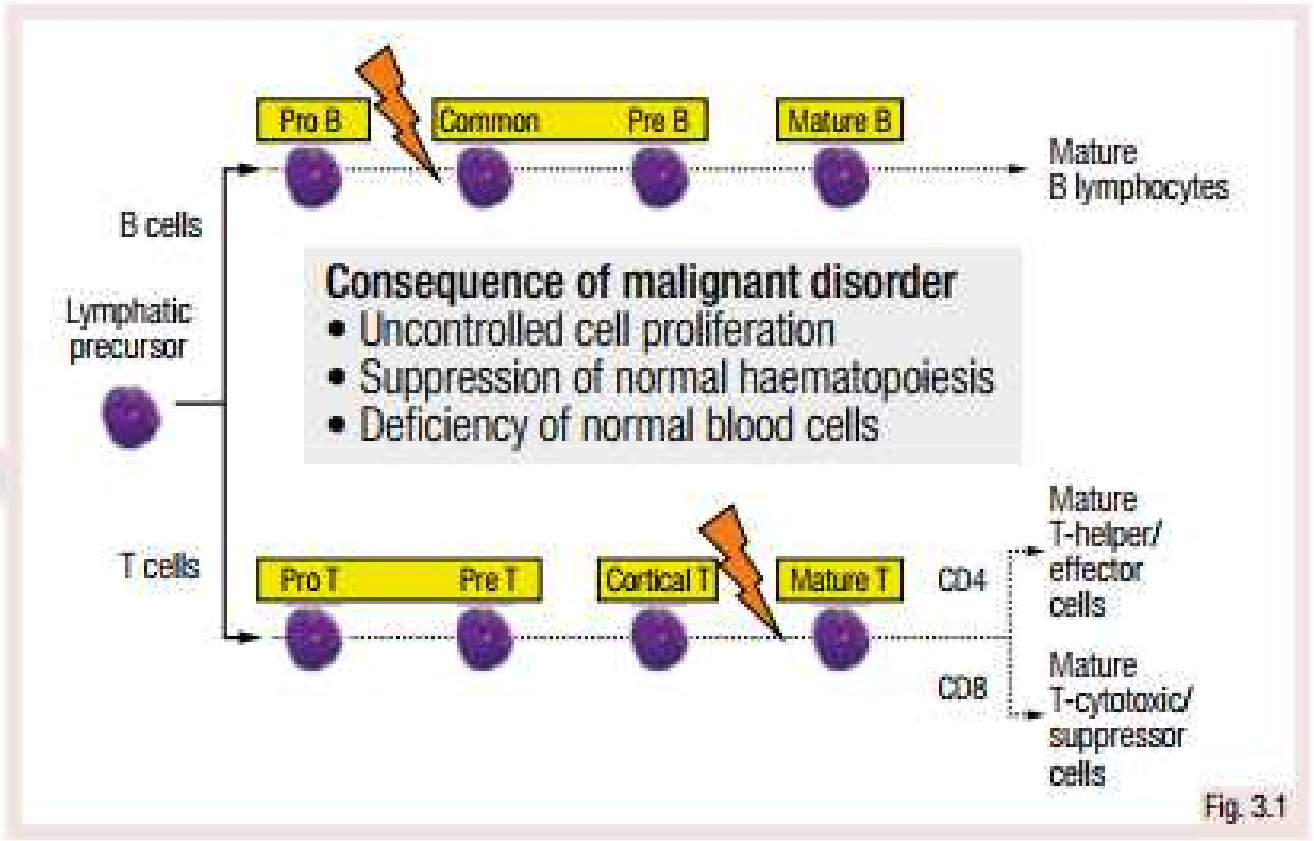

Pro B
Common
Pre B
Mature B
Mature
B lymphocytes
B cells
Lymphatic
precursor
Consequence of malignant disorder
• Uncontrolled cell proliferation
• Suppression of normal haematopoiesis
• Deficiency of normal blood cells
T cells
Pro T
Pre T
Cortical T
Mature T
CD4
CD8
Mature
T-helper/
effector
cells
Mature
T-cytotoxic/
suppressor
cells

Fig. 3.1

Leukaemia	Main recurrent genetic aberrations in leukaemia in adults (frequency at diagnosis ≥5%)	
	Chromosomal aberrations	Gene mutations
ALL	Hyperdiploidy Hypodiploidy *t(9;22)/BCR-ABL1* *t(4;11)/MLL-AF4* Deletions of 9p incl. *CDKN2A/B* (9p21.3) *t(1;19)/TCF3-PBX* *t(12;22)/EP300-ZNF384*	*FAT1, SF1, CRLF2, TET2, PTPN11, CREBBP, MLL2, PAX5, SETD2, FLT3, RUNX1, DIS3, MPL, NRAS, KRAS, JAK2* *IKZF1* deletions and mutations *NOTCH1, FBXW7, JAK3, DNM2* (specifically in T-ALL)
AML	*t(8;21)/RUNX1-RUNX1T1* *inv(16)* or *t(16;16)/CBFB-MYH11* *t(15;17)/PML-RARA* Deletions of: 7q, 5q	*NPM1, DNMT3A, CEBPA, TET2, IDH1, IDH2, FLT3-ITD* (internal tandem duplication), FLT3-TKD (tyrosine kinase domain), *MLL*-PTD (partial tandem duplication), *ASXL1, NRAS, KRAS, TP53, WT1, PTPN11, RUNX1*
CLL	Deletions of: 13q14, 11q23, 17p Trisomy of chromosome 12 Rearrangements involving: 3p21, 11q23, 13q14, 14q32 and 18q21	*NOTCH1, ATM, PAX5, SF3B1, BIRC3, CHD2, TP53*
CML	*t(9;22)/BCR-ABL1*	*ABL1*-TKD (tyrosine kinase domain) Cause resistance to TKI; Not extensively studied for other mutations at diagnosis

Fig. 11.4

ALL, Acute lymphoblastic leukaemia; AML, acute myeloid leukaemia;
CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia;
T-ALL, T cell acute lymphoblastic leukaemia; TKI, tyrosine kinase inhibitor.

TABLE 1. Common Chromosomal and Molecular Abnormalities in B-Cell ALL

Cytogenetics	Gene	Incidence in Adults	Incidence in Children
Hyperdiploidy (> 50 chromosomes)	—	7%	25%–30%
t(12;21)(p13;q22)	*ETV6-RUNX1 (TEL-AML1)*	2%	22%–25%
t(9;22)(q34;q11): Philadelphia chromosome	*BCR-ABL1*	25%	2%–4%
t(4:11)(q21;q23) and other *KNMT2A* translocations	*KNMT2A*	8%–10%	2%–3% (60%–80% in infants)
Low hypodiploid near triploid	*TP53* in low hypodiploid	8%–10%	2%–3%
t(1;19)(q23;p13)	*TCF3-PBX1*	3%	4%
t(11;14)(q11), e.g., (p13;q11), (p15;q11)	*TCRα* and *TCRδ*	20%–25%	10%–20%
BCR-ABL1-like, Philadelphia-like	Various	10%–30%	15%
Ikaros	*IKZF1*	25%–35%	12%–17%

DeAngelo, DJ, Jabbour, E, Advani A, "Recent Advances in Managing Acute Lymphoblastic Leukemia," American Society of Clinical Oncology Educational Book 2020 :40, 330-342

Acute leukemia

- KMT2A (MLL gene, 11q23)
- Presence of rearrangement is associated with poor prognosis
- 60-80% of infants
- 2-3% of children; 8-10% of adults
- Rarely express CD10
- CD19, CD15 or CD65 positive

Acute leukemia

- TCF3-PBXI
- t(1:19)
- Favorable outcome with intensive therapy
- Philadelphia-like subgroup transcription profile
- 20% of young adult and adult B-cell leukemia
- 24% of older adults
- Lack t(9;22) BCR-ABL1 rearrangement
- Poor prognosis

Acute leukemia

- Hypodiploid
- Includes near haploid (24-31 chromosomes) and low hypodiploid (32-39 chromosomes) and high hypodiploid (40-43 chromosomes)
- RAS and PI3K pathways are frequently mutated in near-haploid ALL
- TP53 and IKZF are often mutated in low-hypodiploid ALL
- Poor prognosis

Acute leukemia

- Older patients express high levels of CFRL2
- Low hypodiploidy or near triploidy, complex cytogenetics, IKZF1 mutations, chromosome 17 abnormalities, and KMT2A rearrangements are more common in older patients
- High hyperdiploidy is less common in older patients
- Higher incidence of B-cell phenotype in older patients

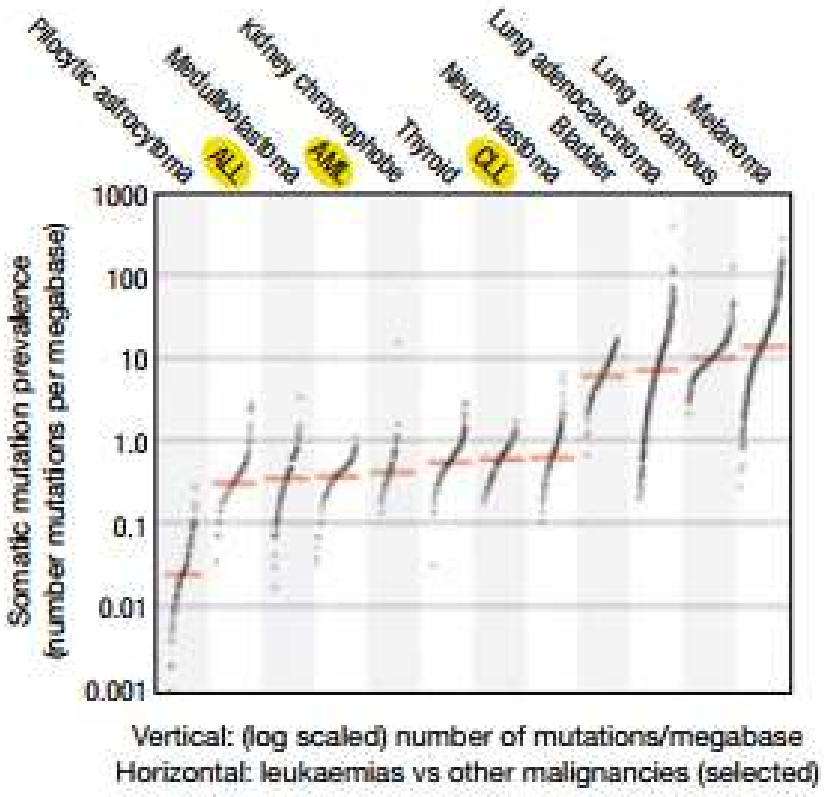


Fig. 11.6

ALL, Acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.

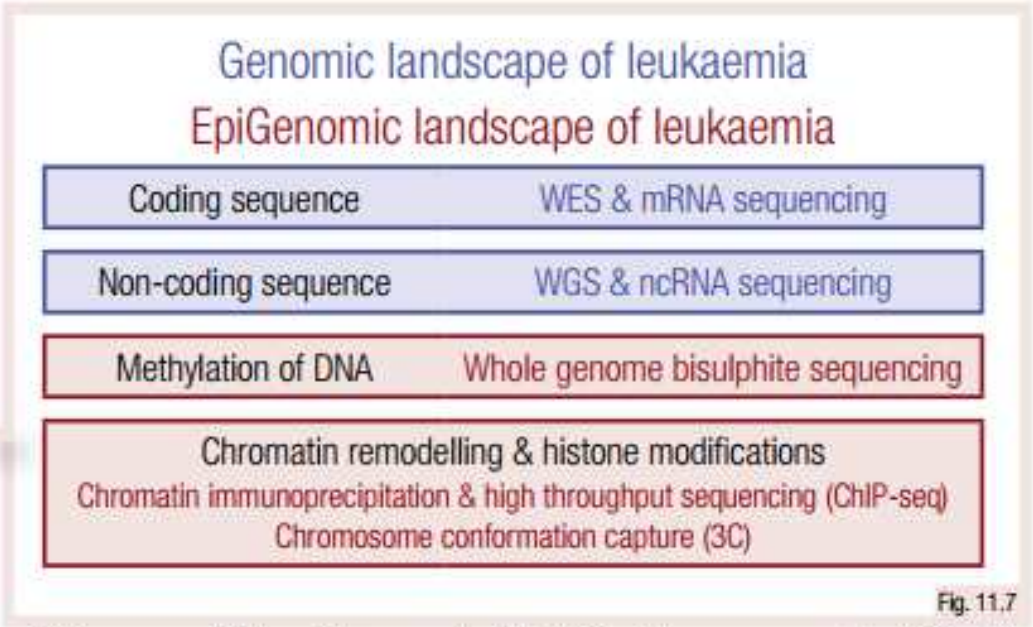


Fig. 11.7

mRNA, messenger RNA; ncRNA, non-coding RNA; WES, whole exome sequencing; WGS, whole genome sequencing.

Acute leukemia

- Hypercellular marrow
- Lymphoblasts
- Mediastinal thymic masses occur in 50% to 70% of T-ALLs, which are also more likely to be associated with lymphadenopathy and splenomegaly.
- 70% NOTCH mutation
- In both B- and T-ALL, the tumor cells have scant basophilic cytoplasm and nuclei somewhat larger than those of small lymphocytes.
- The nuclear chromatin is delicate and finely stippled, and nucleoli are usually small and often demarcated by a rim of condensed chromatin.

Acute leukemia

- Nuclear membrane is deeply subdivided
- Convoluted nuclear appearance.
- High mitotic rate
- Macrophages ingesting apoptotic tumor cells may impart a “starry sky” appearance
- Symptoms related to depression of marrow function
- Fatigue, fever, bleeding
- Bone pain secondary to neoplastic infiltration of marrow
- Hepatosplenomegaly, testicular enlargement
- Meningeal signs

Acute B-cell leukemia

- 95%, TdT + (DNA polymerase)
- Very immature B-cell lymphoblasts express CD19
- Immature B-cell lymphoblasts express CD10, CD19
- Later mature B-cell lymphoblasts express CD10, CD19, CD20, and IgM
- Mature B-cells do not express CD34 or TdT
- CD20 > 20% is associated with disease resistance and poorer outcomes

Acute lymphocytic leukemia

- Acute leukemia may occur at any age.
- Most common childhood malignancy.
- Stormy onset.
- Fever, anemia, bleeding, bone pain and tenderness, adenopathy, splenomegaly, headache, vomiting, nerve palsies commonly seen.
- Hemorrhage occurs at a later stage.
- Involves all tissues.
- Mediastinal and lymph node involvement are typical of ALL.

Acute lymphocytic leukemia

- CD52 expressed
- Loss of function mutations inPAX5, E2A, and ERF, or balanced t(12;21) involving TEL and AML1.
- PTPN2 mutation.

Acute lymphocytic leukemia

- 90% have numerical or structural changes in the chromosomes of the leukemic cells.
- Most common is hyperploidy (>50 chromosomes).
- Polyploidy, and t(12;21), t(9;22) and t(4;11) translocations also found.
- These alterations correlate with immunophenotype and sometimes predict prognosis.

Acute lymphocytic leukemia

- Favorable prognostic markers include age of 2 to 10 years, low white count, an early pre-B phenotype, and hyperploidy or t(12;21).
- Trisomy 4, 10, 17,and TEL gene re-arrangement are also favorable prognostic markers in childhood B-cell progenitor disease.
- In order of increasing risk are t(1;19), t(4;11), and t(9:22).

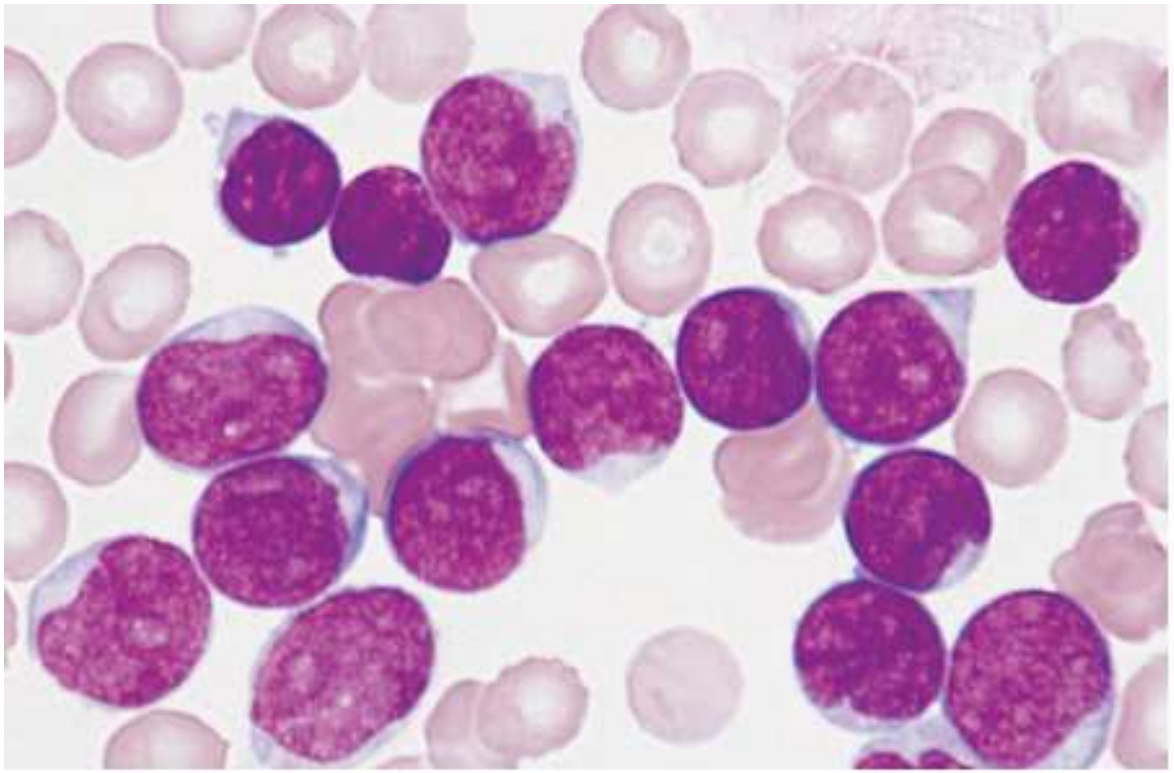
Acute lymphocytic leukemia

- Poor prognosis markers include age under 2
- Strong association of infantile ALL with translocations involving the MLL gene at 11q23
- Presentation in adolescence or adulthood;
- Peripheral blood blast counts greater than 100,000 (high tumor burden);
- Involvement of meninges, mediastinum, or testes/ovaries.
- CD20 expressed in adult ALL indicates poor prognosis.

Acute lymphocytic leukemia

- BCR-ABL1 gene mutation sufficient to lead to CML.
- Requires IKZF1 gene mutation to produce B-cell ALL.
- The Philadelphia chromosome, t(9;22), is present in only 3% of childhood ALL but up to 25% of adult cases.
- Different molecular mechanisms underlie the pathogenesis of pre-B and pre-T ALL.
- No protection against sterility if treated before puberty.
- Puberty will be delayed.
- 44% ovarian failure after chemotherapy
- >50% it total body irradiation utilized.
- High incidence of miscarriages.

Acute lymphocytic leukemia



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Acute lymphocytic leukemia

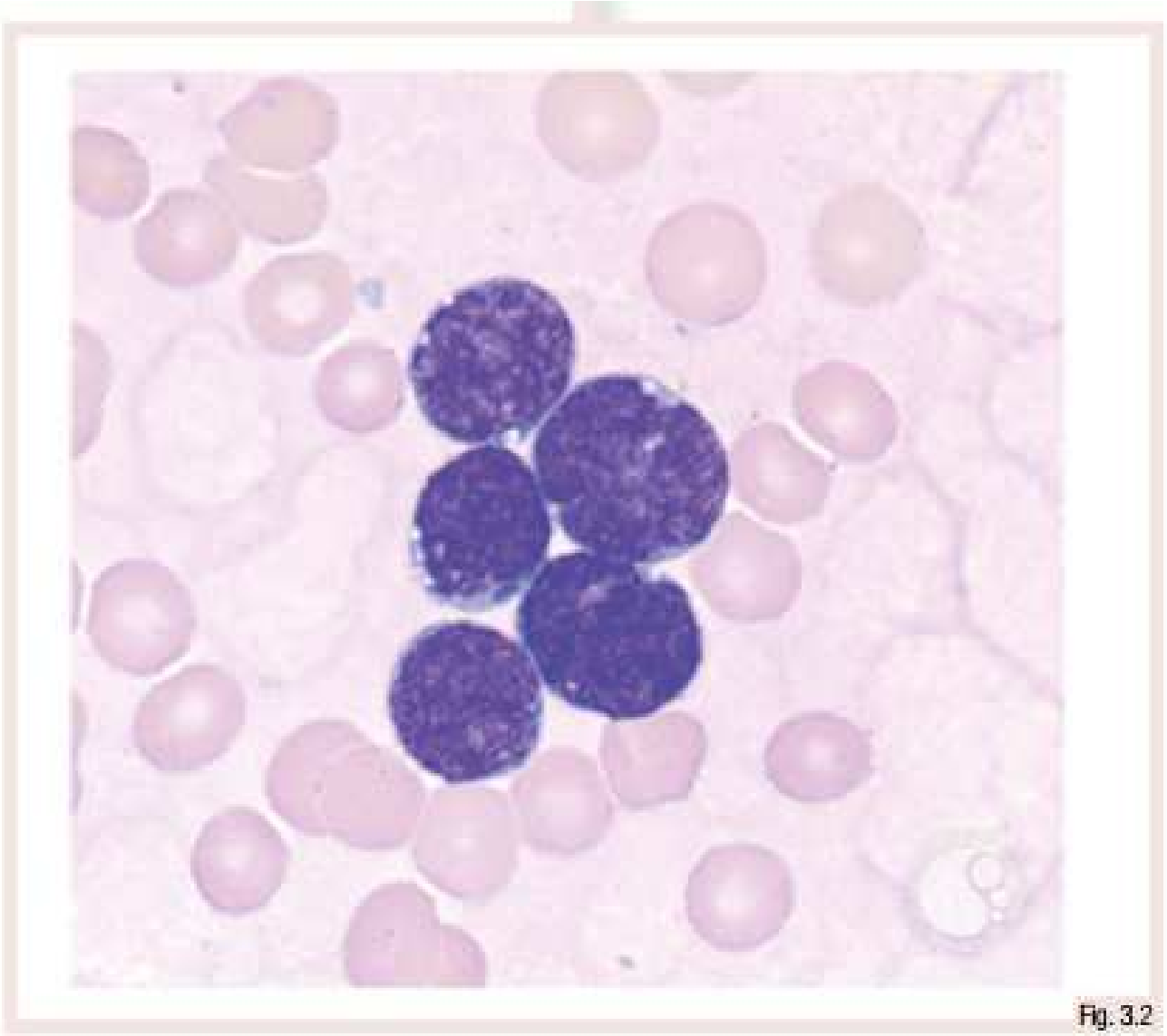


Fig. 3.2

FAB classification no longer employed

Cytology	Immunophenotype		Frequency	Cytogenetics	Molecular genetics
L1/2	T-lineage	TdT+, cyCD3+, CD7+	24%	*t(10;14)*	*HOX11-TCRa/d* *LMO1/2-TCRa/d* *TAL1-TCRa/d*
	Early	CD2-, sCD3-, CD1a-	6%	*t(11;14)*	
	Thymic	sCD3±, CD1a+	12%	*t(1;14)*	
	Mature	sCD3+, CD1a-	6%	p15,16 ab.	
L1/2	B-lineage	HLA-DR+,TdT+,CD19+	76%		
	Pro	CD10-	11%	— *t(4;11)*	— *ALL1(MLL)-AF4*
	Common	CD10+	49%	— *t(9;22)*	— *BCR-ABL*
	Pre	CD10±, cyIgM+	12%	— *t(9;22), t(1;19)*	— *BCR-ABL,E2A-PBX1*
L3	Mature	TdT±, CD10±, sIgM+	4%	— *t(8;14)*	— *cMYC-IgH*

HLA-DR+, Human leukocyte antigen-DR-positive.

Fig. 3.3

Complete remission

- Definition of CR in bone marrow
- Complete hematological remission: <5% blasts
- MRD: 1%-0.01% blasts
- Complete molecular remission: <0.01% blasts

Probability of continuous complete remission in GMALL trials (including SCT)

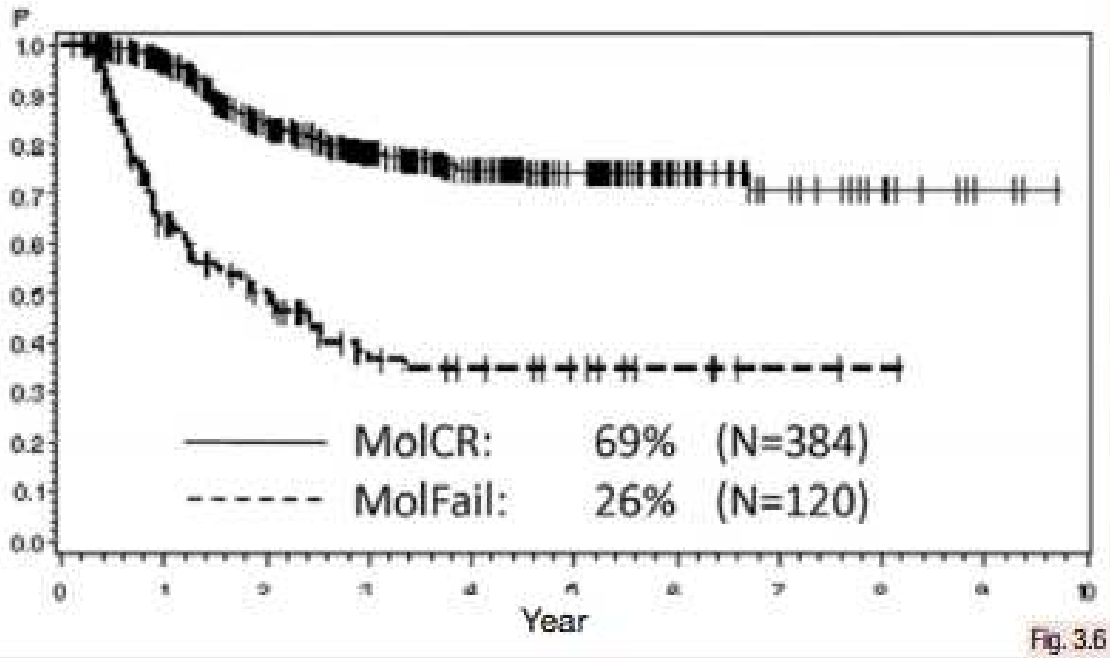


Fig. 3.6

GMALL, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; MolCR, molecular complete remission; MolFail, molecular failure; SCT, stem cell transplantation.

Hairy cell leukemia

- 2% of leukemias
- Median age 55 years
- Men 5:1
- Generally present with splenomegaly
- >50% have pancytopenia
- Hairy cells have round, oblong, or reniform nuclei and moderate amounts of pale blue cytoplasm with thread-like or bleb-like or hair-like extensions that are best recognized with phase-contrast microscopy
- In the bone marrow, the cells are enmeshed in reticulin

Hairy cell leukemia

- BRAF VE600 mutation
- Express CD19, CD20, Ig (usually IgG)
- Distinctive markers are:
- CD11c, CD25, CD103, and annexin A1
- Indolent

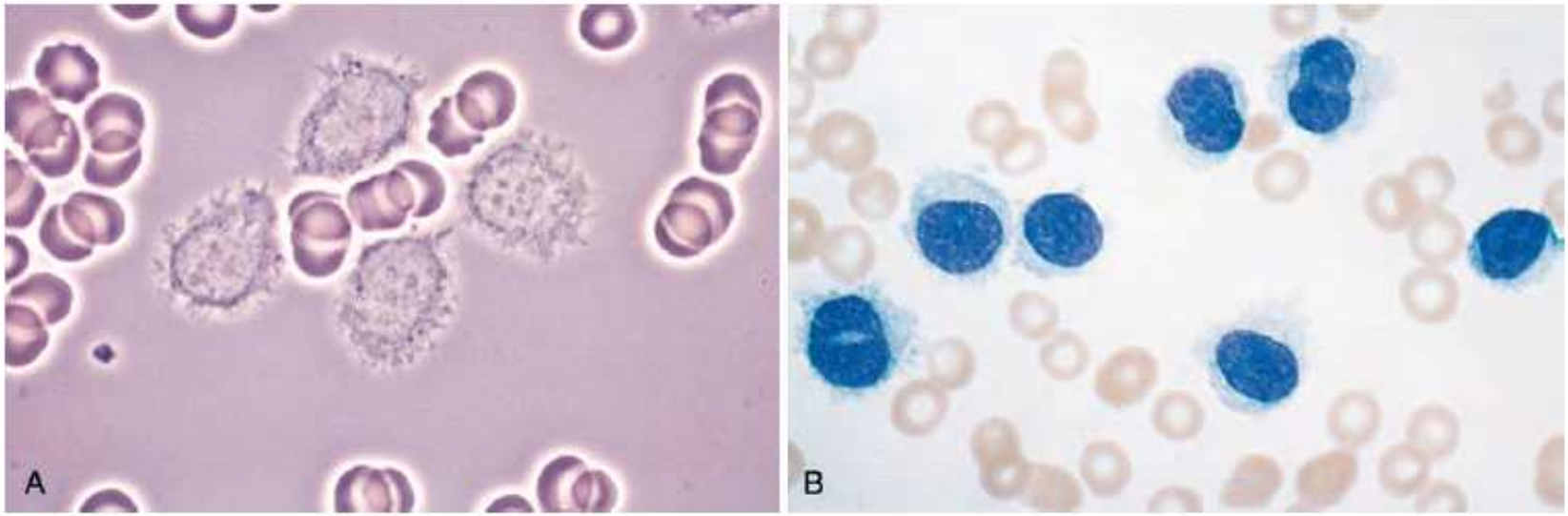


Figure 13-21 Hairy cell leukemia (peripheral blood smear). **A,** Phase-contrast microscopy shows tumor cells with fine hairlike cytoplasmic projections. **B,** In stained smears, these cells have round or folded nuclei and modest amounts of pale blue, agranular cytoplasm.

Acute T-cell leukemia

- TdT+
- The more immature T-cell tumors are usually negative for surface CD3, CD4, and CD8, CD1, CD2, CD5, and CD7.
- “Late” pre–T-cell tumors are positive for these markers.
- T-cell ALL may be associated with mediastinal compression secondary to thymus enlargement

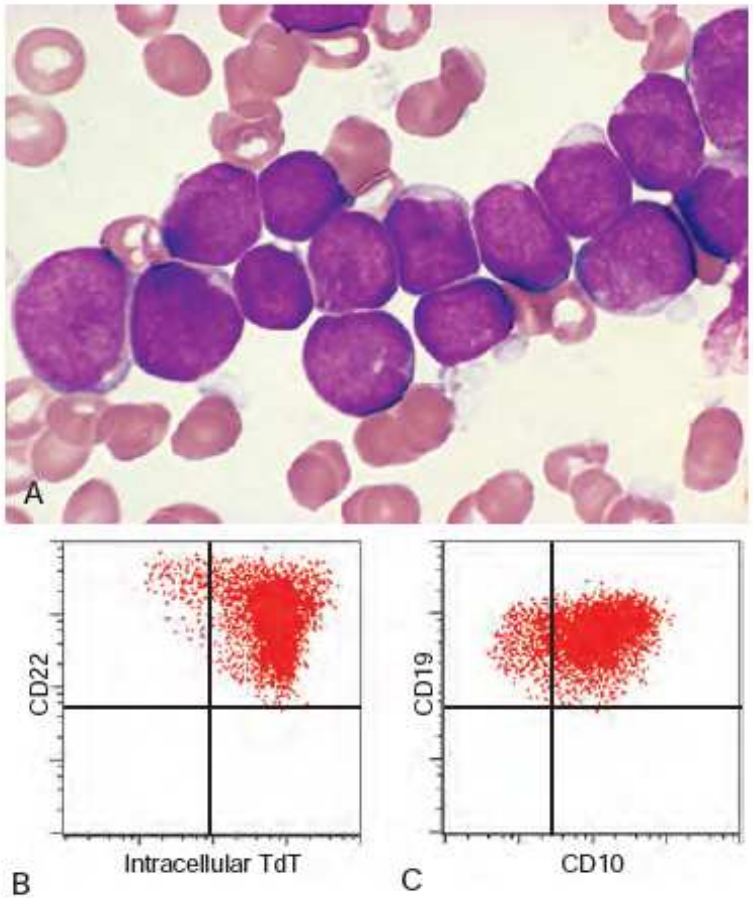


Figure 13-6 **A,** Acute lymphoblastic leukemia/lymphoma. Lymphoblasts with condensed nuclear chromatin, small nucleoli, and scant agranular cytoplasm. **B** and **C** represent the phenotype of the ALL shown in **A,** analyzed by flow cytometry. **B,** Note that the lymphoblasts represented by the red dots express terminal deoxynucleotidyl-transferase (TdT) and the B-cell marker CD22. **C,** The same cells are positive for two other markers, CD10 and CD19, commonly expressed on pre-B lymphoblasts. Thus, this is a B-ALL. (**A,** Courtesy Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas; **B** and **C,** courtesy Dr. Louis Picker, Oregon Health Science Center, Portland, Ore.)

Chronic lymphocytic leukemia

- Chronic lymphocytic leukemia (CLL) and small cell lymphocytic lymphoma (SLL) differ only in the degree of peripheral blood lymphocytosis.
- Deletions of 13q14.3, 11q, and 17p, and trisomy 12q
- Arise from naïve B-cells or post-germinal center memory B-cell
- Express CD19, CD20, CD23, and CD5
- May be asymptomatic
- When symptomatic (e.g., fatigue), 50-60% have generalized lymphadenopathy and hepatosplenomegaly

Chronic lymphocytic leukemia

- The blood contains large numbers of small round lymphocytes with scant cytoplasm
- Some of these cells are usually disrupted in the process of making smears, producing so-called smudge cells.
- The bone marrow is almost always involved by interstitial infiltrates or aggregates of tumor cells.
- Infiltrates are also virtually always seen in the splenic white and red pulp and the hepatic portal tracts

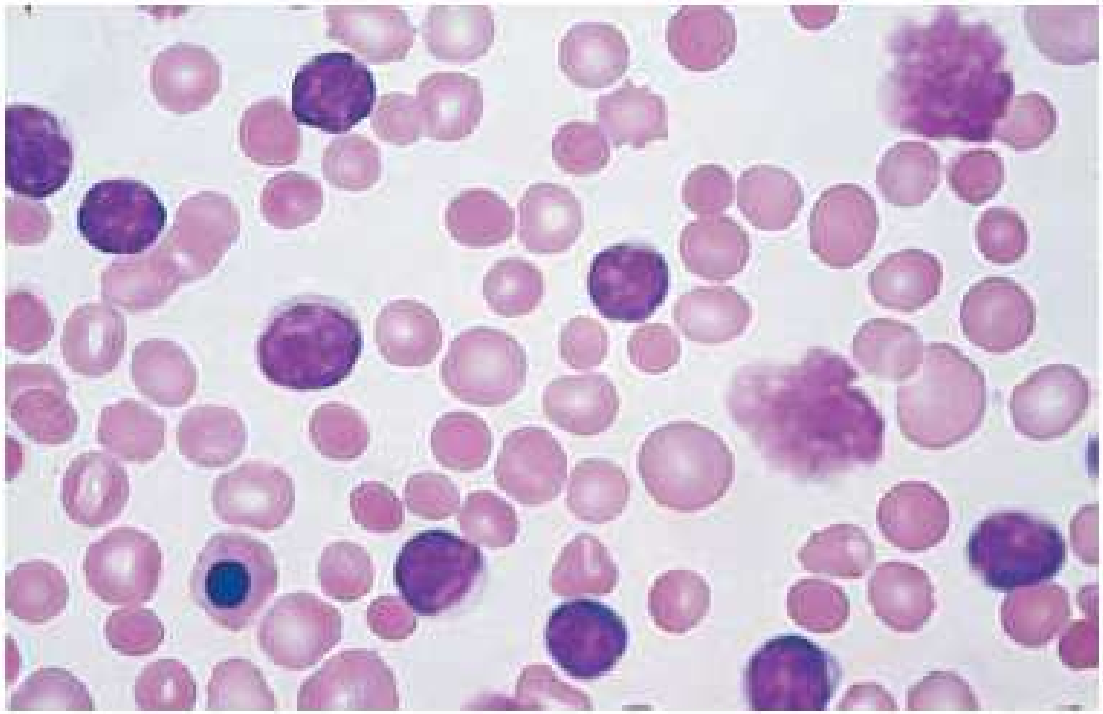


Figure 13-8 Chronic lymphocytic leukemia. This peripheral blood smear is flooded with small lymphocytes with condensed chromatin and scant cytoplasm. A characteristic finding is the presence of disrupted tumor cells (smudge cells), two of which are present in this smear. A coexistent autoimmune hemolytic anemia (Chapter 14) explains the presence of spherocytes (hyperchromatic, round erythrocytes). A nucleated erythroid cell is present in the lower left-hand corner of the field. In this setting, circulating nucleated red cells could stem from premature release of progenitors in the face of severe anemia, marrow infiltration by tumor (leukoerythroblastosis), or both.

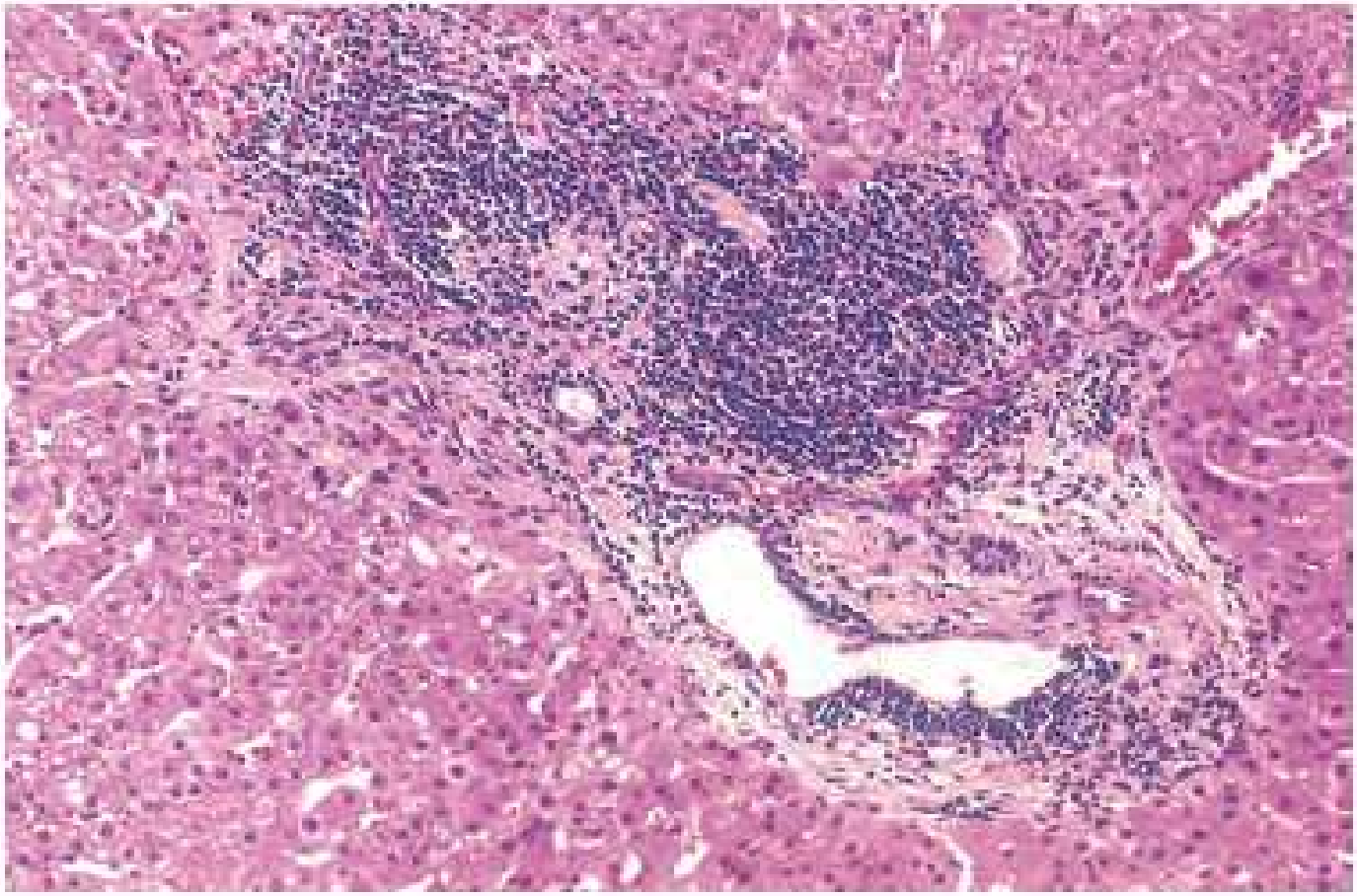


Figure 13-9 Small lymphocytic lymphoma/chronic lymphocytic leukemia involving the liver. Low-power view of a typical periportal lymphocytic infiltrate. (Courtesy Dr. Mark Fleming, Department of Pathology, Children's Hospital, Boston, Mass.)

Chronic lymphocytic leukemia

- Monoclonal B cell lymphocytosis occurs in 4-5% of healthy adults
- Progression to CLL 1-2%/year.
- With same immunophenotype.
- B-cell absolute lymphocyte count distinguishes the two disorders.
- May be familial.
- HCV as host factor
- 28% of HCV+ patients have Monoclonal B-cell Lymphocytosis.
- Prolymphocytic leukemia more likely than CLL to have large atypical lymphocytes in peripheral blood
- Binet staging prognostic

Chronic lymphocytic leukemia

- Median age 60 years old.
- Twice as frequent in men.
- No relation to previous radiation exposure
- No correlation with HLA I
- HLA Class II not expressed on resting T cells
- Higher incidence in first degree relatives

Chronic lymphocytic leukemia

- Often asymptomatic.
- When symptoms appear, they are nonspecific:
- Easy fatigability, weight loss, and anorexia.
- Gradual enlargement of all lymph nodes.
- 50-60%, generalized lymphadenopathy and hepatosplenomegaly
- Leukemia if lymphocytosis. Else, SLL.
- Anemia, and later, thrombocytopenia develop.

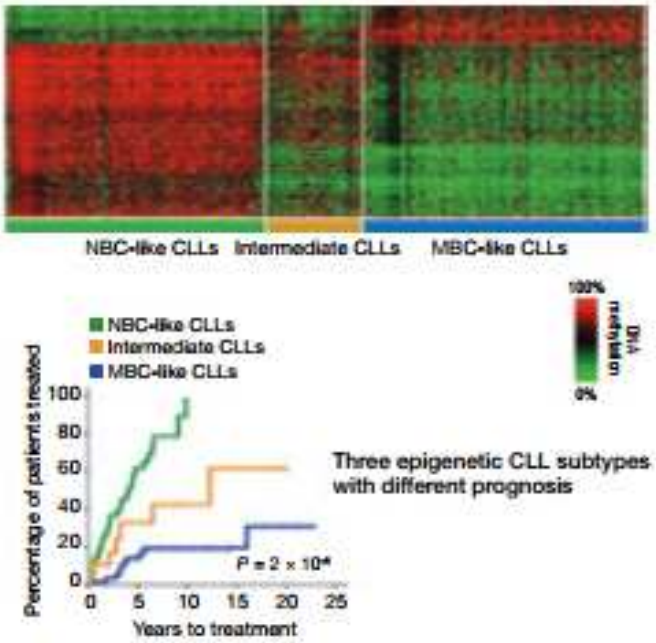


Fig. 11.9

CLL, Chronic lymphocytic leukaemia; MBC, memory B cell; NBC, naïve B cell.

CLL STAGING SYSTEMS

Rai System[a]

Stage	Description	Modified Risk Status
0	Lymphocytosis, lymphocytes in blood >5 x 10^9/L clonal B cells and >40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0–I with splenomegaly, hepatomegaly, or both	Intermediate
III[c]	Stage 0–II with hemoglobin <11.0 g/dL or hematocrit <33%	High
IV[c]	Stage 0–III with platelets <100,000/mm^3	High

Binet System[b]

Stage	Description
A	Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm^3 and <3 enlarged areas
B	Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm^3 and ≥3 enlarged areas
C[c]	Hemoglobin <10 g/dL and/or Platelets <100,000/mm^3 and any number of enlarged areas

Cytogenetics risk categories

Risk	Cytogenetics
High	del 17p (particularly if p53 mutation)
	del 11q (ataxia-telangiectasia mutation)
	Immunoglobulin heavy chain not mutated
	CD38+
	ZAP-70+
	Lymphocyte doubling <than 6 months
	β-2 microglobulin >3.5 mg/L
Intermediate	Trisomy 12
Low	del 13q
	Immunoglobulin chain mutated
	No cytogenetic abnormality

PROGNOSTIC INFORMATION FOR CLL/SLL[a]

TP53 and Immunoglobulin Heavy-Chain Variable (*IGHV*) Region Gene Mutation

	Favorable	Unfavorable
DNA sequencing[b]		
TP53	Wild-type	Mutated
IGHV	>2% mutation	≤2% mutation

Interphase Cytogenetics (FISH)[c]

Unfavorable	Neutral	Favorable
del(11q) del(17p)	Normal +12	del(13q) (as a sole abnormality)

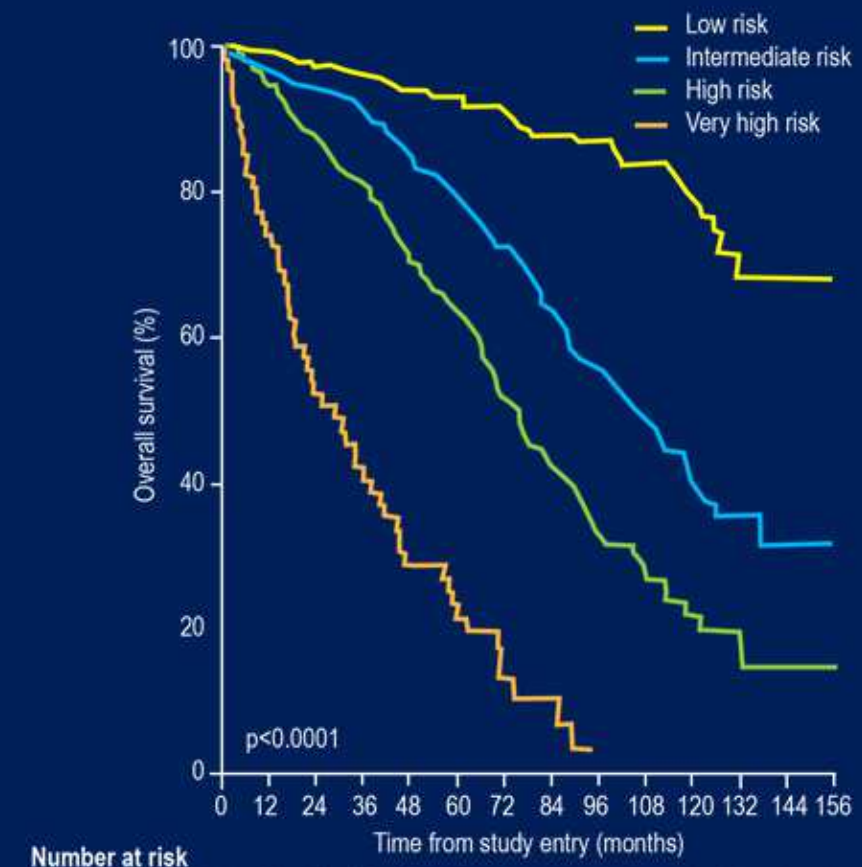
Complex Karyotype[d]

Unfavorable
≥3 unrelated chromosome abnormalities in more than one cell on karyotype

CLL: International Prognostic Index

- 3,472 treatment-naïve patients
- Five independent prognostic factors
  - TP53 deletion and/or mutation
  - IGHV mutational status
  - Serum b2-microglobulin
  - Clinical stage
  - Age: < vs >65 years

CLL-IPI category	OS at 5 years (%)	Potential clinical consequence
Low risk	93.2	Do not treat
Intermediate risk	79.3	Do not treat except if the disease is really symptomatic
High risk	63.3	Treatment indicated except if the disease is asymptomatic
Very high risk	23.3	If you need to treat, do not use chemotherapy but rather novel agents or treatments in clinical trials.



Number at risk

Low risk	341	339	331	320	279	270	224	169	118	81	40	20	8	0
Intermediate risk	474	452	441	415	352	312	232	143	83	52	27	13	5	1
High risk	337	314	284	256	205	178	120	69	40	19	12	4	1	0
Very high risk	62	46	31	25	16	13	5	3	0	--	--	--	--	--

IGHV = immunoglobin heavy chain variable region

International CLL-IPI working group. *Lancet Oncol.* 2016;17:779-790.

Chronic lymphocytic leukemia

- Chronic lymphocytic leukemia (small cell lymphocytic lymphoma) has a distinctive immunophenotype.
- The tumor cells express the pan B-cell markers CD19 and CD20.
- CD23 and CD5, the latter a T-cell marker that is expressed on only a small subset of normal B cells, are present on the tumor cells.
- There is also typically low level expression of

Chronic lymphocytic leukemia

- There is also typically low level expression of surface immunoglobulin heavy chain (usually IgM or IgM and IgD) and either κ or λ light chain.
- IVGH mutational status does not change over time.
- PI_3K constitutively activated.

Chronic lymphocytic leukemia

- Those of naïve B-cell origin (no somatic hypermutation of Ig segments) are more aggressive than those of post-germinal memory B-cell origin.
- Patients with small cell lymphoctytic lymphoma and marrow involvement can be leukopenic.
- Patients with chronic lymphocytic leukemia and heavy tumor burdens can have leukocyte counts in excess of 200,000 /uL.
- A small monoclonal immunoglobulin "spike" is present in the serum of some patients.
- Immunoglobulin levels, however, may be depressed.

Chronic lymphocytic leukemia

- Lymphocyte doubling time short
- Associated with poor survival:
- Elevated β2M level
- Elevated STK (salvage pathway of DNA synthesis)
- Elevated ANG-2 (blood vessel destabilizing Tie2 ligand
- Elevated sCD23+, CD49d+ (α4 integrin)

Chronic lymphocytic leukemia

- CD38 is an ectoenzyme that metabolizes extracellular nucleotides for use in cells
- Increases cytoplasmic concentrations of Ca^{2+}
- Interacts with CD31 on vessels
- Close association with zap70 and Ki67 expression as well as IgVH mutation.
- There is overexpression of VEGF and the antiapoptotic protein MCL 1

Chronic lymphocytic leukemia

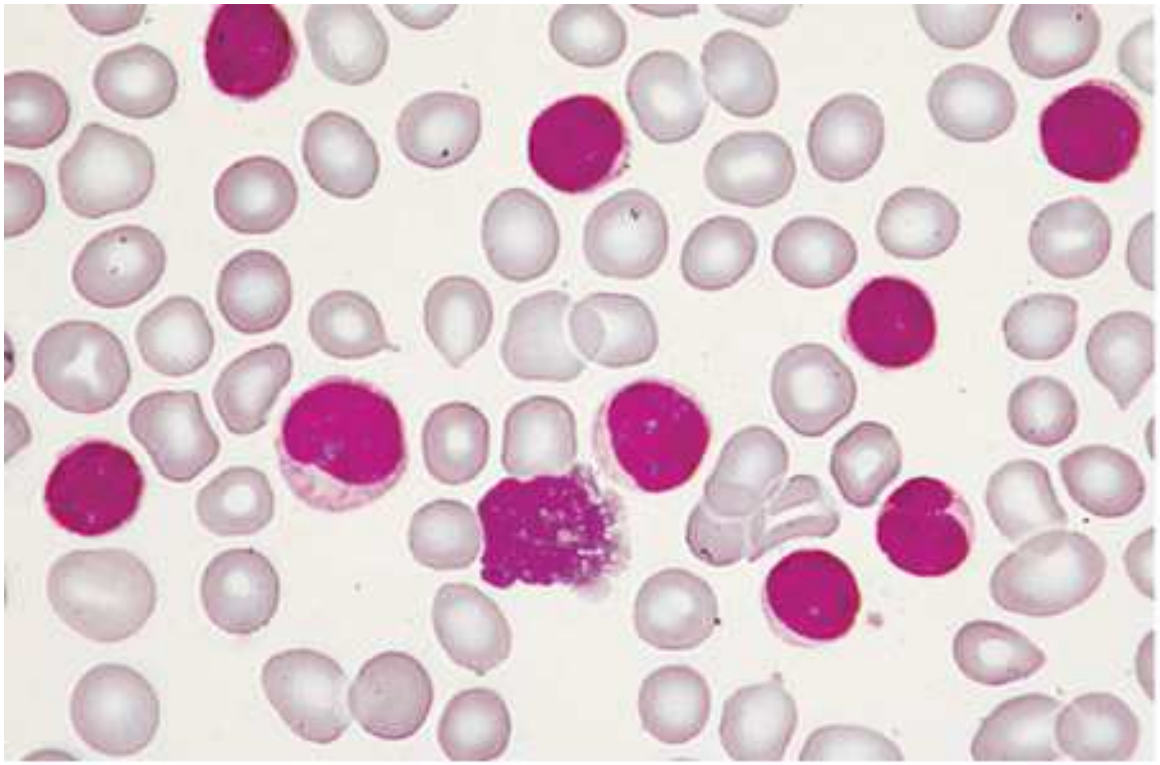


Fig. e11-46 Accessed 02/01/2010

Biomarkers in CLL

Biomarker	Time to first therapy	Remission duration	Therapy guidance
ZAP70 (>20%)	Short (3-4 years)		
IgV_H unmutated	Short		More rapid progression if ZAP70 negative as well
CD38 (>30%)	Good predictor		
Del 17p13.1	Short	Very Short	Stem cell transplantaion
Del 11q22.3	Short	Short	Fludaribine, cyclophosphamide, rituximab
Complex FISH	Short	Short	Stem cell transplantation
Complex karyotype	Short	Short	Stem cell transplantaion

Adults

CYTOGENETIC RISK GROUPS FOR B-ALL

RISK GROUPS	CYTOGENETICS
Good risk	• Hyperdiploidy (51–65 chromosomes) ▸ Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome • t(12;21)(p13;q22): *ETV6-RUNX1*[a]
Poor risk	• Hypodiploidy[b] (<44 chromosomes) • *KMT2A* rearranged (t[4;11] or others) • t(v;14q32)/IgH • t(9;22)(q34;q11.2): *BCR-ABL1* (defined as high risk in the pre-TKI era) • Complex karyotype (5 or more chromosomal abnormalities) • Ph-like ALL; intrachromosomal amplification of chromosome 21 (*iAMP21*)

Children

GENETIC RISK GROUPS FOR B-ALL

RISK GROUPS	GENETICS[a]
Favorable risk features	• **High hyperdiploidy (51–67 chromosomes)** ▸ Trisomy of chromosomes 4, 10, and 17 are among trisomies that have the most favorable outcome • **Cryptic t(12;21)(p13;q22):** ***ETV6-RUNX1*** **fusion**
Unfavorable risk features	• **Hypodiploidy (<44 chromosomes)**[b,c] • ***KMT2Ar*** **(t[4;11] or others)** • **t(9;22)(q34;q11.2):** ***BCR-ABL1*** • ***BCR-ABL1*****–like (Ph-like) ALL** ▸ **JAK-STAT (*CRLF2r*,[d] *EPORr, JAK1/2/3r, TYK2r*, mutations of *SH2B3, IL7R, JAK1/2/3*)** ▸ **ABL class (rearrangements of *ABL1, ABL2, PDGFRA, PDGFRB, FGFR*)** ▸ **Other (*NTRKr, FLT3r, LYNr, PTK2Br*)** • **t(17;19):** ***TCF3-HLF*** **fusion** • **Intrachromosomal amplification of chromosome 21 (*iAMP21*)** • **Alterations of *IKZF1*[e,f]**

Acute precursor B-cell lymphocytic leukemias

- B-cell precursor lymphocytic leukemia cells expresses TdT but lack surface immunoglobulin.
- CD19 highly expressed (20% of lymphoblasts). CD22 expressed both on membrane and in cytoplasm.
- t(12;21) is the most common abnormality. Affects CBFα and ETV6.
- B-cell prolymphocytic leukemia transformation occurs in 15%-30% of patients.

Acute precursor B-cell lymphocytic leukemias

- Prolymphocytic transformation is marked by worsening of cytopenias, increasing splenomegaly, and the appearance in the peripheral blood of large numbers of cells with a large nucleus containing a single prominent, centrally placed, nucleolus (prolymphocytes).
- Prolymphocytic leukemia more likely than chronic lymphocytic leukemia to have large atypical lymphocytes in peripheral blood
- When >55% of the cells are prolymphocytes, the diagnosis of is confirmed.

Acute precursor B-cell lymphocytic leukemias

- Men 4:1
- Splenomegaly
- No adenopathy

Acute precursor B-cell lymphocytic leukemias

- t(11;14) translocation may also be found (bcl-1 oncogene in proximity to immunoglobulin heavy chain gene.
- Transformation to diffuse large B-cell lymphoma (Richter syndrome) occurs in 10% of patients. Transformation to diffuse large B-cell lymphoma is often heralded by the appearance of a rapidly enlarging mass within a lymph node or the spleen.
- T-cell form associated with inv 14 (q11;q32), trisomy 8q. Bcl-3 oncoprotein expressed. TCR gene rearrangements noted.

Acute precursor T-cell leukemia

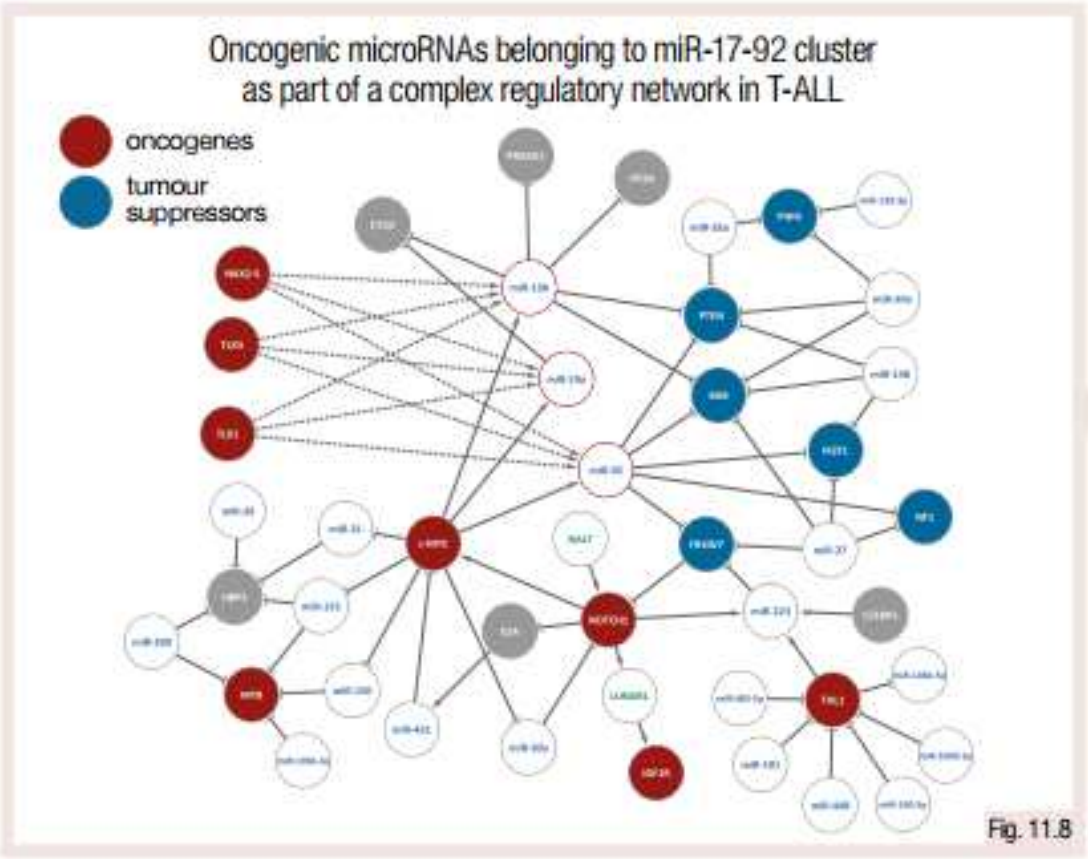
- High risk
- Precursor cell expresses TdT.
- TAL1 most common rearrangement (T-cell receptor locus).
- May be CD79a+
- CD1a-, CD8-
- May be CD5+
- DNMT3A and other myeloid-specific mutations may be present
- 70% of T-cell leukemias have NOTCH 1 gain of function mutation.

Adult T-cell leukemia

- HTLV1 associated
- Southern Japan, West Africa, Caribbean
- Generalized lymphadenopathy, hepatosplenomegaly, peripheral blood lymphocytosis, and hypercalcemia.
- Cells with multilobated nuclei (“cloverleaf” or “flower” cells) are frequently observed
- Generally rapidly progressive
- May also be associated with demyelinating disease of the central nervous system and spinal cord

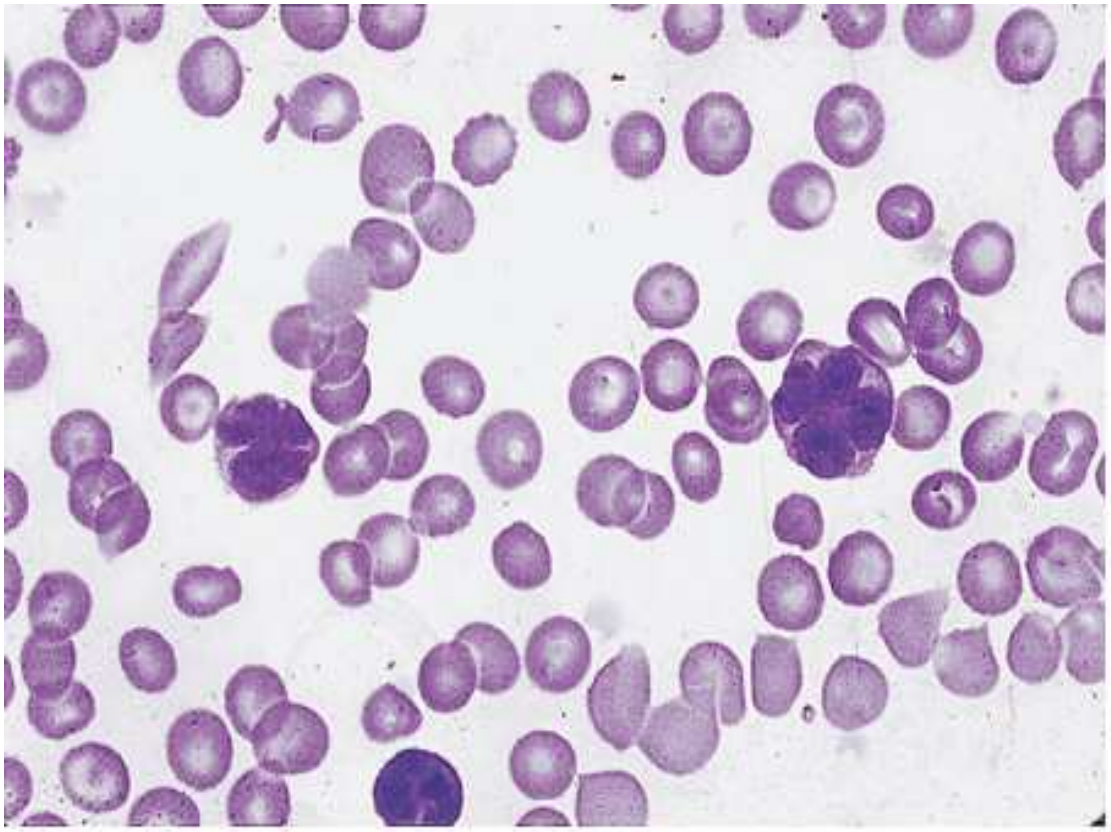
Adult T-cell leukemia

- Notch receptor mutations (activation) in T-ALL.
- Expresses CD25 (IL-2 receptor) as well as CD52.
- CD1a positivity with the absence of CD13 expression is associated with improved survival.
- No need for radiation therapy to CNS



T-ALL, T cell acute lymphoblastic leukaemia.

Acute T cell leukemia



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Leukemia cells with typical "flower-shaped" nucleus. Less commonly, multinucleated giant cells resembling Reed-Sternberg cells may be present. The tumor cells contain clonal HTLV-1 provirus.

Fig. e11-48 Accessed 02/01/2010

Mycosis fungoides

- Mycosis fungoides is a tumor of CD4+ lymphocytes that presents with an inflammatory premycotic phase and progresses through a plaque phase to a tumor phase.
- Neoplastic T cells infiltrate the epidermis and upper dermis. The T cell nucleus is cerebriform.
- Disease progression is characterized by extracutaneous spread, most commonly to lymph nodes and bone marrow. Small numbers of circulating tumor cells can also be identified in peripheral smears in up to 25% of cases in the plaque or tumor phase.

Sézary syndrome

- A neoplasm of CD4+ lymphocytes.
- CLA adhesion molecule and chemokine receptors CCR4 and CCR 10 expressed, leading to homing on skin.
- Skin involvement is manifested as a generalized exfoliative erythroderma. In contrast to mycosis fungoides, the skin lesions rarely proceed to tumefaction.
- Circulating tumor cells have cerebriform nuclei.
- Indolent. May transform into large T-cell lymphoma as a terminal event.
- There is a marked overlap with mycosis fungoides.

Sézary's syndrome

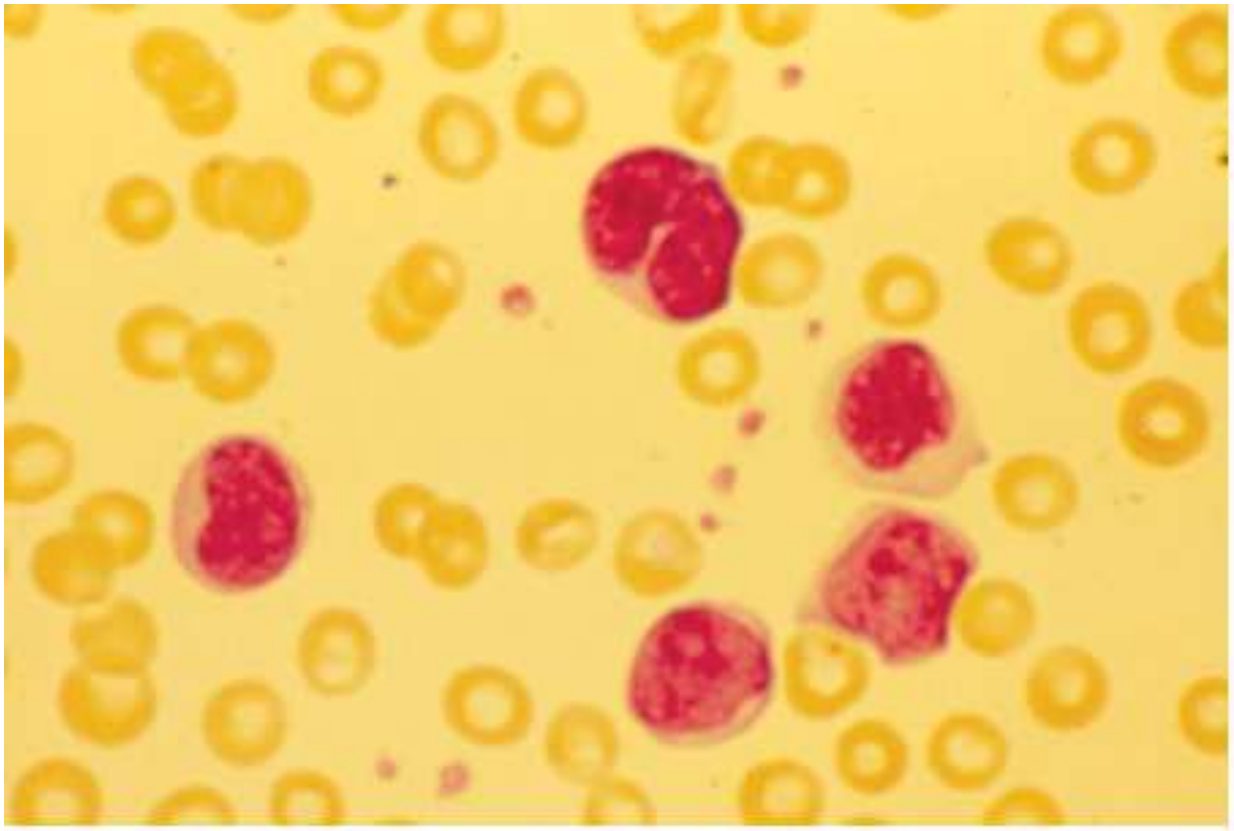


Fig. e11-47
Accessed
02/01/2010

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Large granular lymphocytic leukemia

- Lymphocytes in the peripheral blood and bone marrow contain abundant blue cytoplasm with a scattering of coarse blue granules.
- Marrow involvement is usually focal, without physical displacement of normal hematopoietic elements. The splenic red pulp and hepatic sinusoids are also usually infiltrated.
- Neutropenia and anemia dominate the clinical picture. Neutropenia is often accompanied by a striking decrease in late myeloid forms in the bone marrow.

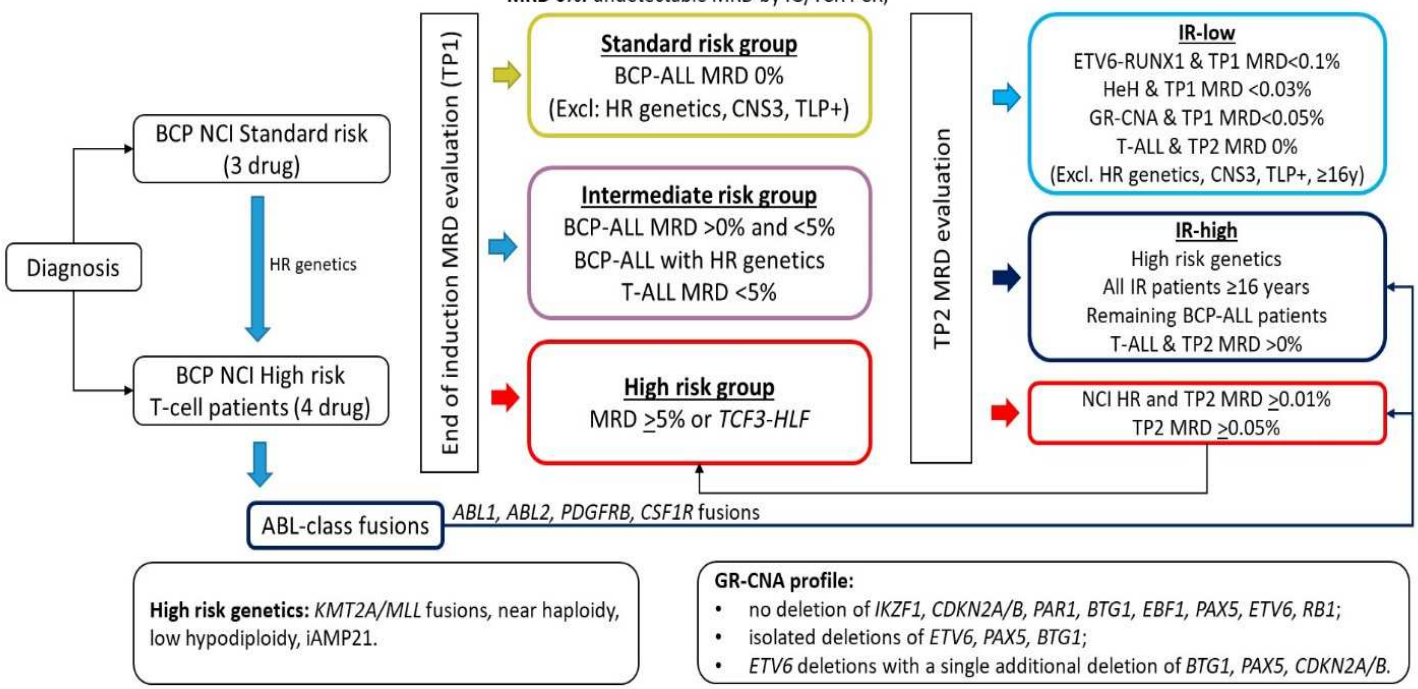
Large granular lymphocytic leukemia

- Less commonly, large granular lymphocytic leukemia is associated with pure red cell aplasia.
- An increased incidence of rheumatologic disorders has also been observed in large granular lymphocytic leukemia (Felty syndrome).
- Cytokine activation of STAT3
- T cell form indolent (CD3+).
- NK (CD3-, CD56+) form aggressive.

Immunologic classification of morphologically indistinct leukemia

	B-lymphocyte	**T-lymphocyte**	**Myeloid**
Pathognomonic	Surface IgM+	CD3+ TCR+	MPO+
High likelihood	CD19+ CD20+ CD10+ CD79a+	CD2+ CD5+ CD8+ CD10+	CD17+ CD13+ CD33+ CD65+
Suggestive	TdT CD24+	TdT CD7+ CD1a+ CD79a+	CD14+ CD15+ CD64+

Risk stratification algorithm



High risk genetics: *KMT2A/MLL* fusions, near haploidy, low hypodiploidy, iAMP21.

GR-CNA profile:

- no deletion of *IKZF1, CDKN2A/B, PAR1, BTG1, EBF1, PAX5, ETV6, RB1*;
- isolated deletions of *ETV6, PAX5, BTG1*;
- *ETV6* deletions with a single additional deletion of *BTG1, PAX5, CDKN2A/B.*

THERAPY

Treatment

- Imatinib in BCR-ABL-positive ALL and rituximab in CD20- positive ALL.
- Ponatinib is the only drug suitable for a T315I mutation.
- SCT is an essential part of ALL management
- ALL at relapse has a poor prognosis with remission rates of only 40% for first salvage and a median survival of 6 months.

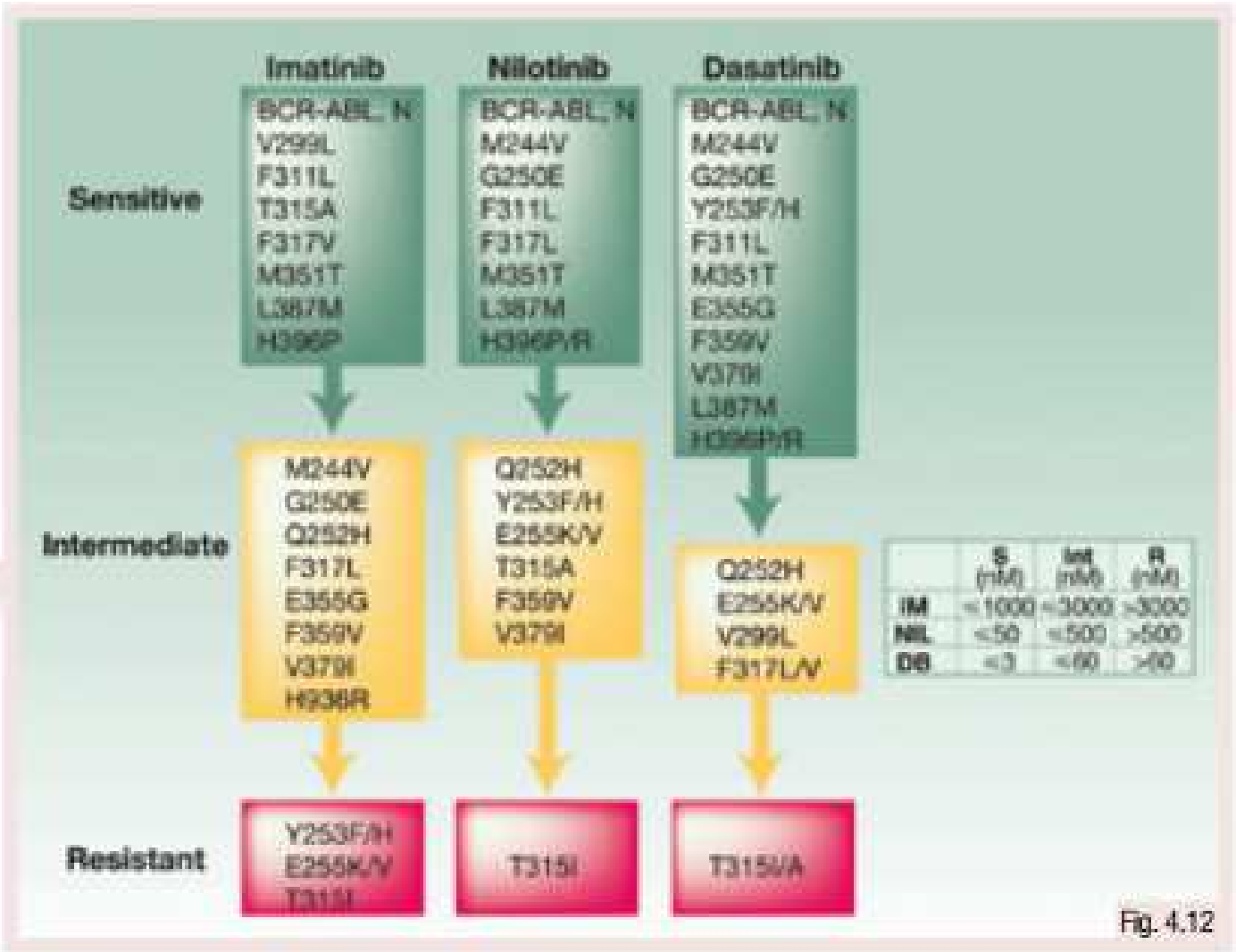


Fig. 4.12

DB, Dasatinib; IM, imatinib; NIL, nilotinib.

RISK STRATIFICATION DEFINITIONS[a]
INITIAL RISK GROUP STRATIFICATION

	Low Risk	Standard Risk	High Risk	Very High Risk
Children's Oncology Group (COG) (B-ALL only)	N/A	Age 1 to <10 y and WBC <50,000/mm^3	• Age ≥10 y and/or WBC ≥50,000/mm^3 • CNS-3/testicular disease[b] • *BCR-ABL1* is considered HR feature (see PEDALL-5) • Steroid pre-treatment	N/A
St. Jude Consortium	• B-ALL with DNA index ≥1.16, *ETV6-RUNX1* fusion OR • B-ALL with age 1–9.9 y and presenting WBC count <50,000/mm^3 • Absence of standard risk features	• B-ALL with age ≥10 years or presenting WBC count ≥50,000/mm^3 (not DNA index ≥1.16 or *ETV6-RUNX1* fusion) OR • B-ALL with the following features: ▸ CNS-3 status[b] ▸ Overt testicular leukemia ▸ Adverse genetic features[c] OR • T-ALL	N/A	
Dana-Farber Cancer Institute (DFCI) ALL Consortium[d]	N/A	• B-ALL • Age 1 to <15 y and WBC count <50,000/mm^3 • Absence of HR/VHR adverse biologic features	• T-ALL • iAMP21 • *BCR-ABL1* is considered HR feature (see PEDALL-5)	• *IKZF1* deletion • *KMT2A*-rearrangement • Low hypodiploidy or near haploidy (ie, hypodiploidy <40 chromosomes) • *TCF3-HLF* (t[17;19])

RISK STRATIFICATION DEFINITIONS[a]
POST-INDUCTION THERAPY RISK GROUP STRATIFICATION

	Low Risk	Standard Risk	High Risk
COG[e] Initial Standard Risk (B-ALL only)	• NCI SR (standard risk), favorable cytogenetics,[f] and CNS-1 or CNS-2[b] • Day 8 peripheral blood MRD <1%, Day 29 end induction (EOI) bone marrow MRD <0.01%	• NCI SR, favorable cytogenetics,[f] and CNS-1 or CNS-2[b] • Day 8 peripheral blood MRD >1%, EOI bone marrow MRD <0.01% (*ETV6/RUNX1*) OR <0.1% double trisomy (DT) OR • NCI SR • Neutral cytogenetics[g] • CNS-1[b] • EOI bone marrow MRD <0.01%	• NCI SR • CNS-2[b] • Neutral cytogenetics[g] • EOI bone marrow MRD (positive or negative) OR • NCI SR • CNS-1 or CNS-2[b] • Unfavorable cytogenetics[f] • EOI bone marrow MRD (positive or negative) OR • NCI SR • CNS-1 or CNS-2[b] • Any cytogenetics • EOI bone marrow MRD >0.01% or >0.1% (DT)
COG[e] Initial High Risk (B-ALL only)	• NCI HR (high risk) but <10 y • Favorable cytogenetics[f] • CNS-1[b] • EOI bone marrow MRD <0.01%		• NCI HR • CNS-1, CNS-2, or CNS-3[b] • Any cytogenetics • EOI bone marrow MRD (positive or negative) OR • NCI SR • CNS-3[b] • Any cytogenetics • EOI bone marrow MRD (positive or negative)

RISK STRATIFICATION DEFINITIONS[a]
POST-INDUCTION THERAPY RISK GROUP STRATIFICATION

	Low Risk	Standard Risk	High Risk	Very High Risk
St. Jude Consortium	• B-ALL with DNA index ≥1.16, *ETV6-RUNX1* fusion OR • B-ALL with age 1–9.9 y with presenting WBC count <50,000/mm^3 AND • Absence of standard or high-risk features	B-ALL with age ≥10 y or presenting WBC count ≥50,000/mm^3 (not DNA index ≥1.16 or *ETV6-RUNX1* fusion) OR B-ALL with the following features: • CNS 3 status[b] • Overt testicular leukemia (evidenced by ultrasonogram) • Adverse genetic features[c] • Poor early response (≥1% MRD on Day 15 of remission induction or ≥0.01% MRD at the end of remission induction) OR • T-ALL • Absence of high-risk features	• MRD ≥1% at the end of remission induction • MRD ≥0.1% at the end of early intensification and inadequate decrease in MRD levels after 1–2 courses of consolidation treatment • Increasing MRD level at ≥0.01% after remission induction • Hypodiploid and MRD ≥0.01% at the end of remission induction • Re-emergence of leukemic lymphoblasts by MRD at ≥0.01% in patients previously MRD negative • Persistently detectable MRD at ≥0.01% after reinduction II	
DFCI ALL Consortium[h]	Initial standard risk with low MRD (<10^{-4}) at end-induction	Initial high risk with low MRD (<10^{-4}) at end-induction	• Initial low risk OR initial high risk • High end-induction MRD (≥10^{-4}) but low MRD (<10^{-3}) end-IB phase	Any of the following: • Initial very-high-risk biology regardless of MRD • Any initial risk group with high end-IB phase MRD (≥10^{-3}) • Patients with M2 marrow at end-induction but in morphologic CR at end-IB phase (regardless of end-IB phase MRD)

PRINCIPLES OF SYSTEMIC THERAPY[a,b]

Regimens for Ph-Negative B-ALL

See Evidence Blocks on PEDALL-F (EB-1)

Regimen Components and Risk Stratification Applications on PEDALL-F (3 of 12)

Preferred	Other Recommended Regimens
• Clinical trial	• Standard arm of COG AALL1731 regimen[c] (based on COG AALL0932 regimen[1]) • Standard arm of COG AALL1732 regimen[c] (based on COG AALL1131 regimen[2,3]) • DFCI ALL Protocol 16-001[c] (based on DFCI ALL protocol 11-001[4]) • Total Therapy XVII regimen[c] (based on Total Therapy XVI regimen[5])

Regimens for Ph-Like B-ALL

See Evidence Blocks on PEDALL-F (EB-2)

Regimen Components and Risk Stratification Applications on PEDALL-F (4 of 12)

Preferred	Other Recommended Regimens
• Clinical trial	• COG AALL1131 regimen[2,3] + dasatinib[6] • COG AALL1521 regimen ± ruxolitinib[c] • DFCI-ALL Protocol 16-001 + dasatinib[c] • Total Therapy XVII regimen + dasatinib[7] • Total Therapy XVII regimen ± ruxolitinib[c,7]

Regimens for Ph-Positive B-ALL

See Evidence Blocks on PEDALL-F (EB-3)

Regimen Components and Risk Stratification Applications on PEDALL-F (5 of 12)

Preferred	Other Recommended Regimens
• Clinical trial	• Standard arm of COG AALL1631[c] (based on COG AALL1122/EsPhALL regimen): imatinib or dasatinib[c]; combined with an HR backbone of the Berlin-Frankfurt-Münster regimen[8] • COG AALL0622 regimen[9]: dasatinib; post-induction intensified chemotherapy based on POG/CCG regimens[10,11] • Total Therapy XVII regimen plus dasatinib on day 15[c]

PRINCIPLES OF SYSTEMIC THERAPY[a,b]

Regimens for T-ALL[d,e,f]

See Evidence Blocks on PEDALL-F (EB-4)

Regimen Components and Risk Stratification Applications on PEDALL-F (6 of 12)

Preferred	Other Recommended Regimens
• Clinical trial	• COG AALL1231 regimen • COG AALL0434 regimen[12] • DFCI-ALL Protocol 16-001[c] (based on DFCI ALL protocol 11-001[4]) • SJCRH regimen based on Total Therapy XVII Regimen[c]

Regimens for Infant ALL

See Evidence Blocks on PEDALL-F (EB-4)

Regimen Components and Risk Stratification Applications on PEDALL-F (6 of 12)

Preferred Regimens	Other Recommended Regimens
• Clinical trial	• Interfant regimens[13-15]

Regimen Components[a,g]

The regimen components outlined in these tables represent the most recently published studies.

Ph-Negative ALL	Induction	Consolidation
COG AALL0932 regimen[16] (SR)	SR arm: dexamethasone, vincristine, pegaspargase; IT therapy: cytarabine then methotrexate	SR-Low/Avg arm: 6-MP,[b] vincristine; IT therapy: methotrexate
		SR-Avg/High arm: cyclophosphamide, cytarabine, 6-MP,[b] vincristine, pegaspargase; IT therapy: methotrexate
COG AALL01131 regimen[17] (HR)	HR arm: prednisone or dexamethasone, vincristine, pegaspargase, daunorubicin; IT therapy: cytarabine then methotrexate	HR arm: cyclophosphamide, cytarabine, 6-MP,[b] vincristine, pegaspargase; IT therapy: methotrexate
DFCI ALL Protocol 11-001[18]	Prednisone, vincristine, pegaspargase, doxorubicin, IT cytarabine, then triple IT therapy (ITT)[a]	SR arm: high-dose methotrexate, vincristine, pegasparagase, 6-MP,[b] dexamethasone; IT therapy: methotrexate or ITT[a]
		HR/VHR[h] arms: high-dose methotrexate, vincristine, pegasparagase, 6-MP,[b] dexamethasone, doxorubicin, dexrazoxane; IT therapy: methotrexate or ITT[a]
Total Therapy XVI regimen[5]	Prednisone, vincristine, daunorubicin, pegaspargase, cyclophosphamide, cytarabine, 6-mercaptopurine (6-MP),[b] age-adjusted ITT[a]	LR arm: high-dose methotrexate, 6-MP,[b] ITT[a]
		SR/HR arm: high-dose methotrexate, 6-MP,[b] ITT[a]

Risk groups: low risk (LR), standard risk (SR), high risk (HR), very high risk (VHR).

Regimen Components[a,g]

Ph-like B-ALL	Induction	Consolidation
COG AALL1131 regimen + dasatinib[c,2,6]	Vincristine, dexamethasone, or prednisone, daunorubicin, pegaspargase; IT therapy: cytarabine then methotrexate	For *CRLF2*- with *ABL* class kinase fusion: cyclophosphamide, cytarabine, 6-MP,[b] vincristine, pegaspargase, + dasatinib; IT therapy: methotrexate
COG AALL1521 regimen ± ruxolitinib[c,19]		For *CRLF2*+ or *CRLF2*- with *JAK2* fusions, *EPOR* rearrangements, *SH2B3* alterations, *IL7R* insertions/deletions: cyclophosphamide, cytarabine, 6-MP,[b] vincristine, pegaspargase, + ruxolitinib; IT therapy: methotrexate
DFCI-ALL Protocol 16-001 + dasatinib[c]	For *ABL* class kinase fusion: DFCI-ALL Protocol 16-001 VHR arm: dexamethasone, vincristine, pegaspargase, doxorubicin, cyclophosphamide, cytarabine, 6-MP[b] + dasatinib; IT therapy: cytarabine then ITT[a] or methotrexate	For *ABL* class kinase fusion: high-dose methotrexate, 6-MP,[b] dexamethasone, vincristine, cyclophosphamide, etoposide, high-dose cytarabine, pegaspargase, doxorubicin + dasatinib; IT therapy: methotrexate
Total Therapy XVII regimen + dasatinib[7] **or Total Therapy XVII regimen ± ruxolitinib**[c,7]	• For *ABL* class kinase fusion: Total Therapy XVII regimen + dasatinib[7] • For mutations associated with JAK-STAT pathway activation: Total Therapy XVII regimen + ruxolitinib	• For *ABL* class kinase fusion: Total Therapy XVII regimen (either LR or SR/HR arm) + dasatinib[7] • For mutations that are associated with JAK-STAT pathway activation: Total Therapy XVII regimen (SR/HR arm) + ruxolitinib

Risk groups: low risk (LR), standard risk (SR), high risk (HR), very high risk (VHR).

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,g]

Ph-positive ALL	Induction	Consolidation
Standard arm of COG AALL1631[c] (based on COG AALL1122/EsPhALL regimen): imatinib or dasatinib[c]; combined with an HR backbone of the Berlin-Frankfurt-Münster regimen[8]	Cyclophosphamide, 6-MP,[b] cytarabine, methotrexate, imatinib/dasatinib	• Dexamethasone, vincristine, methotrexate, ifosfamide, cytarabine, pegaspargase, cyclophosphamide, prednisone, daunorubicin, 6-thioguanine (6-TG),[b] imatinib/dasatinib • HR patients (defined by high MRD after IB phase and/or after HR Consolidation blocks): allogeneic HSCT in CR1
COG AALL0622 regimen + dasatinib[9]	• Prednisone or dexamethasone, vincristine, pegaspargase, daunorubicin or doxorubicin; IT therapy: methotrexate, hydrocortisone, cytarabine • Include TKI (imatinib or dasatinib) once *BCR-ABL* fusion identified or by Day 15 of induction[11,13]	High-dose methotrexate, vincristine, daunorubicin, cyclophosphamide, pegaspargase, dexamethasone, cytarabine, dasatinib; IT therapy: ITT[a]
		HR patients (defined by high MRD at end-induction [≥1%] or after consolidation 2 [≥0.01%]): allogeneic HSCT in CR1
Total Therapy XVII regimen[c] + dasatinib	Total XVII regimen: prednisone, vincristine, daunorubicin, pegaspargase, cyclophosphamide, cytarabine, 6-MP[b], ITT[a]; dasatinib on day 15	LR arm: high-dose methotrexate, 6-MP,[b] dasatinib; ITT[a]
		SR/HR arm: high-dose methotrexate, pegaspargase, 6-MP,[b] dasatinib; ITT[a]

Risk groups: low risk (LR), standard risk (SR), high risk (HR), very high risk (VHR).

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,g]

T-ALL	Induction	Consolidation
COG AALL1231 regimen[c,i]	Dexamethasone, vincristine, pegaspargase, daunorubicin;[i] IT therapy[a]	Cyclophosphamide, cytarabine, 6-MP,[b] pegaspargase, vincristine[i]; IT therapy[a]
COG AALL0434 regimen[12]	Prednisone, vincristine, pegaspargase, daunorubicin; IT therapy: Age-adjusted cytarabine and methotrexate	Cyclophosphamide, cytarabine, 6-MP,[b] pegaspargase, vincristine, nelarabine; IT therapy: methotrexate
DFCI ALL 16-001[c] based on DFCI-ALL Protocol 11-001	Dexamethasone, vincristine, pegaspargase, doxorubicin; IT therapy: cytarabine then ITT[a]	Cyclophosphamide, cytarabine, 6-MP[b]; IT therapy: methotrexate or ITT[a]
SJCRH regimen based on Total Therapy XVII regimen[c]	Prednisone, vincristine, pegaspargase, cyclophosphamide, daunorubicin, 6-MP,[b] cytarabine;[j] ITT[a]	High-dose methotrexate, 6-MP,[b] pegaspargase; ITT[a]

Infant ALL	Induction	Consolidation[k]
Interfant regimens[13-15]	Prednisone, dexamethasone, vincristine, cytarabine, daunorubicin, pegaspargase, methotrexate; IT therapy: cytarabine, prednisone (if initial CNS involvement, methotrexate, prednisone)	Intermediate risk and HR arms: Chemotherapy consolidation: cyclophosphamide, 6-MP,[b] cytarabine, methotrexate, prednisone, pegaspargase[13] Post-consolidation, and HR arm not undergoing HSCT: dexamethasone, 6-TG,[b] vincristine, cytarabine, daunorubicin, pegaspargase, cytarabine, prednisone, cyclophosphamide, methotrexate, 6-MP[b,13]
		LR arm: Identical approach as pediatric ALL risk-stratified chemotherapy based on genetics and MRD response (see PEDALL-I) or interfant consolidation (see above)

PRINCIPLES OF SYSTEMIC THERAPY

Regimens for Relapsed/Refractory ALL[l,m]

See Evidence Blocks on PEDALL-F (EB-5)

Ph-negative ALL[a]

Preferred	Other Recommended Regimens
• Clinical trial	• UKALL R3 backbone chemotherapy[20] • COG AALL01P2 regimen[21] • ALL-REZ BFM 90 regimen[22] • COG AALL07P1 regimen[23] • Blinatumomab[n,24,25] • Tisagenlecleucel (refractory disease or ≥2 relapses)[p,q,28] ▸ Consider participation in a clinical trial for relapsed/refractory B-ALL targeting CD19, CD22, or other antigens, or for relapse following HSCT ▸ Consider participation in a clinical trial with humanized or fully human CAR T-cell binding domains • Inotuzumab ozogamicin[o,26,27] • Clofarabine-containing regimens (eg, clofarabine, cyclophosphamide, etoposide)[29,30] • Fludarabine-based regimens: FLAG-IDA (fludarabine, cytarabine, G-CSF, ± idarubicin)[31] • High-dose cytarabine-based regimens (eg, high-dose cytarabine, pegaspargase)[32]

Regimens for Relapsed/Refractory ALL[l,m]

Ph-positive ALL[a]

Preferred	Other Recommended Regimens
• Clinical trial	• Backbone chemotherapy + TKI, followed by HSCT after CR achieved • The regimens listed on (PEDALL-F [7 of 12]) for Ph-negative ALL may be considered for Ph-positive ALL with TKIs listed below. • TKIs to consider: ▸ Dasatinib ▸ Imatinib • Blinatumomab (TKI intolerant/refractory)[n,25,33] • Tisagenlecleucel (TKI intolerant/refractory disease or relapse post-HSCT)[p,q,28] • Inotuzumab ozogamicin (TKI intolerant/refractory)[o,26,27]

Regimens for Relapsed/Refractory ALL[l,m]

See Evidence Blocks on PEDALL-F (EB-6)

T-ALL[a]

Preferred	Other Recommended Regimens
• Clinical trial	• Nelarabine-containing regimens: eg, nelarabine, cyclophosphamide, and etoposide[34] • Bortezomib-containing regimen: eg, bortezomib, vincristine, doxorubicin, pegaspargase, and prednisone or dexamethasone[23] • UKALL R3 Block 1: dexamethasone, mitoxantrone, pegaspargase, and vincristine[20] • BFM Intensification Block 1: high-dose methotrexate, high-dose cytarabine, dexamethasone, vincristine, pegaspargase, and cyclophosphamide[22] • Consider TKI-based regimen if *ABL*-class translocation

Adult Ph+ disease

Protocols for AYA Patients
Other Recommended Regimens
EsPhALL regimen: TKI† + backbone of the Berlin-Frankfurt-Munster regimen (cyclophosphamide, vincristine, daunorubicin, dexamethasone, cytarabine, methotrexate, pegaspargase, and prednisone)
TKI† + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone)/alternating with high-dose methotrexate/cytarabine
TKI† + multiagent chemotherapy (daunorubicin/vincristine/prednisone/cyclophosphamide)
TKI† + corticosteroid
TKI† + vincristine/dexamethasone
CALGB 10701 regimen: TKI† + multiagent chemotherapy (dexamethasone, vincristine, daunorubicin, methotrexate, etoposide, and cytarabine)

Protocols for Adult Patients (<65 y)
Other Recommended Regimens
TKI† + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone)/alternating with high-dose methotrexate/cytarabine
TKI† + multiagent chemotherapy (daunorubicin/vincristine/prednisone/cyclophosphamide)
TKI† + corticosteroid
TKI† + vincristine/dexamethasone
CALGB 10701 regimen: TKI† + multiagent chemotherapy (dexamethasone, vincristine, daunorubicin, methotrexate, etoposide, and cytarabine)

Maintenance Regimens
TKI† (for ≥ 1 year) + monthly vincristine/prednisone pulses (for 2–3 years)
TKI† (for ≥ 1 year) + monthly vincristine/prednisone pulses (for 2–3 years)/weekly methotrexate/daily 6-mercaptopurine (6-MP)

Adult Ph+ disease

Other Recommended Regimens
Dasatinib†
Imatinib†
Ponatinib†
Nilotinib†
Bosutinib†
Blinatumomab (TKI intolerant/refractory)
Inotuzumab ozogamicin (TKI intolerant/refractory)
Tisagenlecleucel (patients <26 y & with refractory disease or ≥2 relapses and failure of 2 TKIs)
MOpAD regimen/TKI/rituximab (for CD20-positive disease)

TREATMENT OPTIONS BASED ON *BCR-ABL1* MUTATION PROFILE

Therapy	Contraindicated Mutations[n]
Bosutinib	*T315I, V299L, G250E*, or *F317L*[o]
Dasatinib	*T315I/A, F317L/V/I/C*, or *V299L*
Nilotinib	*T315I, Y253H, E255K/V, or F359V/C/I* or *G250E*
Ponatinib[p]	None

Adult Ph+ disease

Protocols for Older Adult Patients (aged ≥65 y) with Ph-Positive ALL According to Intensity
Low Intensity
TKI†
TKI† + corticosteroid
TKI† + vincristine/dexamethasone
Moderate Intensity
EWALL regimen: TKI† + multiagent chemotherapy (vincristine/dexamethasone/methotrexate/cytarabine/asparaginase)
CALGB 10701 regimen: TKI† + multiagent chemotherapy (dexamethasone, vincristine, daunorubicin, methotrexate, etoposide, and cytarabine)
High Intensity
TKI† + hyper-CVAD with dose-reduced cytarabine to 1 g/m^2

Adult Ph- disease

Preferred Regimens
Blinatumomab (for B-ALL)
Inotuzumab ozogamicin (for B-ALL)
Tisagenlecleucel (for B-ALL; patients <26 years and with refractory disease or ≥2 relapses)
Other Recommended Regimens
Inotuzumab ozogamicin + mini-hyperCVD (cyclophosphamide/dexamethasone/vincristine/ methotrexate/cytarabine) for B-ALL
Nelarabine (for T-ALL)
Nelarabine, etoposide, cyclophosphamide (for T-ALL)
Augmented hyper-CVAD
Vincristine sulfate liposome injection
Clofarabine
Clofarabine, cyclophosphamide, etoposide
MOpAD regimen
MOpAD regimen/rituximab (for CD20-positive disease)
FLAG-IDA regimen (fludarabine, cytarabine, G-CSF ± idarubicin)
FLAM regimen (fludarabine, cytarabine, mitoxantrone)
Cytarabine-containing regimens (eg, high-dose cytarabine, idarubicin, IT methotrexate)
Alkylator combination regimens (eg, etoposide, ifosfamide, mitoxantrone)

Adult Ph- disease

Protocols for Older Adult Patients (aged ≥65 y) with Ph-Negative ALL According to Intensity
Low Intensity
Vincristine/prednisone
Prednisone/vincristine/methotrexate/6-mercaptopurine (POMP)
Moderate Intensity
GMALL regimen: idarubicin/dexamethasone/vincristine/cyclophosphamide/cytarabine ± rituximab
PETHEMA ALLOLD07 regimen: vincristine/dexamethasone/idarubicin/cyclophosphamide/cytarabine/methotrexate/L-asparaginase
GRAALL regimen: doxorubicin/vincristine/dexamethasone/cytarabine/cyclophosphamide
Modified DFCI 91-01 protocol: dexamethasone/doxorubicin/vincristine/methotrexate/cytarabine/L-asparaginase/IT chemotherapy
Inotuzumab ozogamicin + mini-hyperCVD (cyclophosphamide/dexamethasone/vincristine/methotrexate/cytarabine) for B-ALL
High Intensity
Hyper-CVAD with dose-reduced cytarabine to 1 g/m^2
CALGB 9111 regimen: cyclophosphamide/daunorubicin/vincristine/prednisone/pegaspargase

Acute lymphocytic leukemia

- 3% of children with acute lymphocytic leukemia may present with CNS metastases
- Over half will show systemic leukemia.
- CNS prophylaxis (with intrathecal methotrexate or cytosine arabinoside or cranial irradiation) follows.
- Reduces relapse rate from 30% to 5%.
- Neurotoxic.
- Children who receive cranial radiation before age 5 are susceptible to brain tumors and endocrine dysfunction.

Acute lymphocytic leukemia

- Maintenance chemotherapy involves daily mercaptopurine and weekly methotrexate for a period of 2-3 years.
- Constant dosing of methotrexate improves survival.
- Vincristine and prednisone are also utilized in adults.
- Though 90% will achieve remission, cure rates approach 70%.
- Allogeneic bone marrow transplantation in first remission may be curative for 60% of those with high risk disease.

Acute lymphocytic leukemia

- Intensive use of methotrexate and glucocorticoids has led to an increased frequency of aseptic necrosis of bone.
- High dose methotrexate is associated with better outcomes in children.
- Increased risk of venous thromboembolism with use of asparaginase

Acute lymphocytic leukemia

- Infant ALL of mixed lineage are at high risk.
- Burkitt's leukemia responds to high dose induction therapy.
- Successful allogeneic bone marrow transplantation in first remission is associated with cure.
- Relapse after one year may respond to second induction course and transplantation.
- Late CNS relapse (>18 months) responds to chemotherapy.
- Imanitib (tyrosine kinase inhibitor) used if Ph+.
- 17% will develop malignancy secondary to therapy.

Prolymphocytic leukemia

- Treated with an anti-CD20 monoclonal antibody to reduce cell counts
- T-cell form, 20% of cases, may also respond to pentostatin.
- Allogeneic bone marrow transplantation may be curative.

Lymphocytic leukemia

- CD20 upregulated with prednisone
- Potentiate response to rituximab
- CD22 expressed in cytoplasm and membrane of all precursor B-ALL.
- Respond to epratuzumab.
- CD52 expressed in B and T-ALL.
- Respond to alemtuzumab.

Lymphocytic leukemia

- Depletion of asparagine leads to apoptosis in lymphoblasts.
- Effective as well in T-cell leukemia.
- Blocking purine nucleoside phosphorylase leads to T-cell lymphopenia.

Hairy cell leukemia

SUGGESTED TREATMENT REGIMENS[a]

INITIAL THERAPY[b,c,d]

Preferred Regimens
- Purine analogs
  - Cladribine ± rituximab
  - Pentostatin

RELAPSED/REFRACTORY THERAPY[b,d]

	Preferred Regimens	Other Recommended Regimens	Useful Under Certain Circumstances
Less than complete response after initial treatment OR Relapse <2 years	• Clinical trial • Alternative purine analogue + rituximab • Vemurafenib[e]	• Peginterferon-alfa 2a[f] • Alternative purine analogue	• Rituximab, if unable to receive purine analog
Relapse ≥2 years	• Retreat with initial purine analogue + rituximab • Alternative purine analogue + rituximab	• n/a	• Rituximab, if unable to receive purine analog

PROGRESSIVE DISEASE AFTER RELAPSED/REFRACTORY THERAPY[d]

Preferred Regimens	Other Recommended Regimens
• Clinical trial • Moxetumomab pasudotox[g] • Vemurafenib ± rituximab	• Ibrutinib[h]

Hairy cell leukemia

- Responds to cladribine (95% response rate).
- IFN-α as well as 2-deoxycoformycin produce high response rates.
- Splenectomy is reserved for those with thrombocytopenia with bleeding of those for whom systemic chemotherapy has failed.

Indications of when to begin treatment in CLL

- Progressive marrow failure
- Autoimmune anemia.
- Thrombocytopenia poorly responsive to therapy
- Treatment is initiated if weight loss, fever without infection, night sweats, hemoglobin <10.0 g/dl, or bulky lymphadenopathy or splenomegaly.
- Transient localized lymphadenopathy due to infection and hypogammaglobulinemia is not an indication to initiate treatment.
- Lymphocyte doubling time <6 months.

NCI working group treatment guidelines

- Vitamin D deficient patients do more poorly than do those with adequate vitamin D. levels.
- Fit patients have a creatinine clearance >70 ml/min and ECOG performance status 0-2.
- Good risk categories:
- Trisomy 12 and “normal cytogenetics”
- The absence of del13q, del17p, del 11q, and trisomy 12
- Best risk if del 13q.

NCI working group treatment guidelines

- Fludarabine, cyclophosphamide, rituximab for young, fit patients
- May be curative
- Older patients may be treated with ibrutinib, or acalubratinib with or without anti-CD20 antibody, or venetoclax with anti-CD20 antibody

NCI working group treatment guidelines

- Acalabrutinab has fewer side effects than does ibrutinib.
- Atrial fibrillation, hypertension, arthralgias
- If maculopapular rash, hold until rash disappears, then restart
- Venetoclax and rituximab
- High rate of complete remissions and absence of residual disease
- Tumor lysis syndrome a complication
- May use BTK inhibitors if failure

NCI working group treatment guidelines

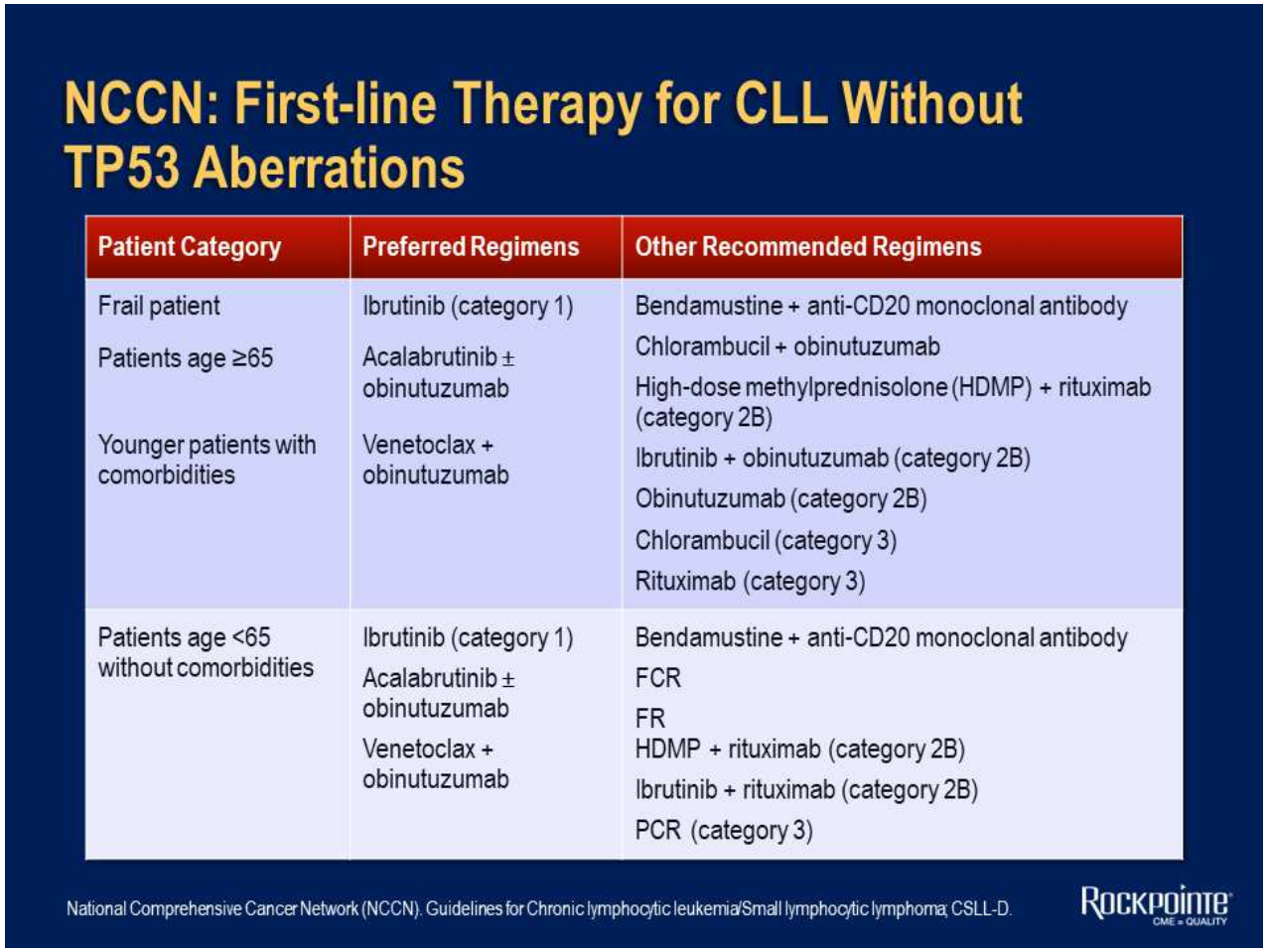
- Intermediate to poor risk category:
- Del 17p mutation:
- Alemtuzumab with or without fludarabine;
- Fludarabine, cyclophosphamide, alemtuzumab, and rituximab;
- Fludarabine, cyclophosphamide, rituximab.
- These regimens are associated with improved responses but with symptomatic CMV infections in some patients.

NCI working group treatment guidelines

- Those patients with significant co-morbidities and no del 17p mutation are offered chlorambucil with or without rituximab or obinutuzumab (both are anti-CD20 antibodies) or dose reduced fludarabine regimens.
- Del11q responds to alemtuzumab if no prior therapy.
- Flavopiridol is a synthetic flavone that inhibits CDK 1,2,9 and induces apoptosis.
- It is p53 independent.
- Effective in poor risk disease (e.g., del17p).

NCI working group treatment guidelines

- Those patients with significant co-morbidities and a del 17p mutation may benefit from high dose methyl-prednisolone plus rituximab.
- Responses are short-lived if not followed by allogeneic stem cell transplant.
- Bendamustine active in high-risk relapsed CLL
- Lenalidomide of use in refractory CLL



The effect of rituximab is lost above 70 years of age.

Treatment of CLL

- Ibrutinib and acalabrutinib (BTK inhibitors) improve progression-free survival in patients with chronic lymphocytic leukemia when used as first line therapy
- This benefit extends across all prognostic groups.
- Time-limited therapy with venetoclax results in deep remissions with undetectable minimal residual disease in a high-proportion of treatment-naïve patients with chronic lymphocytic leukemia.
- Ibrutinib-rituximab in relapsed or refractory Waldenström's macroglobulinemia with or without CXCR4 mutation.

European options

- Alemtuzumab is a humanized antibody that targets CD52 on leukocytes and induces cell lysis.
- Effective in good risk categories (del 13q, trisomy 12) as well as in high risk categories (del17p).
- Benefit in del 11q demonstrated only in naïve patients.
- Ofatumumab is a chimeric anti-CD20 antibody for use in fludarabine and alemtuzumab failures.
- Fab domain binds specifically to both the small and large extracellular loops of the CD20 molecule.
- The Fc domain mediates immune effector functions to result in B-cell lysis in vitro (may be complement mediated or ADCC mediated).

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL without del(17p)/*TP53* mutation
(alphabetical by category)

FIRST-LINE THERAPY[e]		
Frail patient with significant comorbidity (not able to tolerate purine analogs) OR Patients aged ≥65 y and younger patients with significant comorbidities (creatinine clearance [CrCl] <70 mL/min)	Preferred regimens • Acalabrutinib[f] ± obinutuzumab (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g] + obinutuzumab (category 1)	Other recommended regimens • Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) + anti-CD20 monoclonal antibody[d,h] (not recommended for frail patients) • Chlorambucil + obinutuzumab • High-dose methylprednisolone (HDMP) + rituximab (category 2B) • Ibrutinib[f] + obinutuzumab (category 2B) • Obinutuzumab (category 2B) • Chlorambucil (category 3) • Rituximab (category 3)
Patients aged <65 y without significant comorbidities	Preferred regimens • Acalabrutinib[f] ± obinutuzumab (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g] + obinutuzumab	Other recommended regimens • Bendamustine + anti-CD20 monoclonal antibody[d,h,i] • FCR (fludarabine,[j] cyclophosphamide, rituximab)[i,k] (preferred for patients with *IGHV*-mutated CLL) • FR (fludarabine[j] + rituximab)[k,l] • HDMP + rituximab (category 2B) • Ibrutinib[f] + rituximab (category 2B) • PCR (pentostatin, cyclophosphamide, rituximab) (category 3)

POST FIRST-LINE CHEMOIMMUNOTHERAPY MAINTENANCE THERAPY
Other recommended regimen
• Consider lenalidomide for high-risk patients (blood MRD ≥10^{-2} or ≥10^{-4} and <10^{-2} with unmutated *IGHV*)[m] after first-line therapy

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL without del(17p)/*TP53* mutation
(alphabetical by category)

RELAPSED/REFRACTORY THERAPY[e]			
Frail patient with significant comorbidity OR Patients aged ≥65 y and younger patients with significant comorbidities (CrCl <70 mL/min)	**Preferred regimens** • Acalabrutinib[f,n] (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Duvelisib[f] • Idelalisib[f] + rituximab[o]	**Other recommended regimens** • Alemtuzumab[p] ± rituximab • Chlorambucil + rituximab • Reduced-dose FCR[j,k] • HDMP + rituximab • Idelalisib[f] • Lenalidomide[q] ± rituximab	• Obinutuzumab • Ofatumumab • Reduced-dose PCR • Venetoclax[f,g] • Dose-dense rituximab (category 2B) • Bendamustine + rituximab[r] (category 2B) • Bendamustine, rituximab + ibrutinib[f,r] (category 2B) • Bendamustine, rituximab + idelalisib[f,r] (category 3)
Patients aged <65 y without significant comorbidities	**Preferred regimens** • Acalabrutinib[f,n] (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Duvelisib[f] • Idelalisib[f] + rituximab[o]	**Other recommended regimens** • Alemtuzumab[p] ± rituximab • Bendamustine + rituximab • FC[j,k] + ofatumumab • FCR[j,k] • HDMP + rituximab • Idelalisib[f] • Lenalidomide[q] ± rituximab	• Obinutuzumab • Ofatumumab • PCR • Venetoclax[f,g] • Bendamustine, rituximab + ibrutinib[f] (category 2B) • Bendamustine, rituximab + idelalisib[f] (category 2B)

POST SECOND-LINE CHEMOIMMUNOTHERAPY MAINTENANCE THERAPY (for complete or partial response after relapsed or refractory therapy)
Other recommended regimens
• Lenalidomide[m] • Ofatumumab (category 2B)

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL with del(17p)/*TP53* mutation
(alphabetical by category)

FIRST-LINE THERAPY[e]

Preferred regimens	Other recommended regimens
• Acalabrutinib[f] ± obinutuzumab	• Alemtuzumab[p] ± rituximab
• Ibrutinib[f]	• HDMP + rituximab
• Venetoclax[f,g] + obinutuzumab	• Obinutuzumab

RELAPSED/REFRACTORY THERAPY[e]

Preferred regimens	Other recommended regimens
• Acalabrutinib[f,n] (category 1)	• Alemtuzumab[p] ± rituximab
• Ibrutinib[f] (category 1)	• HDMP + rituximab
• Venetoclax[f,g] + rituximab (category 1)	• Idelalisib[f]
• Duvelisib[f]	• Lenalidomide[q] ± rituximab
• Idelalisib[f] + rituximab[o]	• Ofatumumab[s]
• Venetoclax[f,g]	

Richter's transformation

Regimens
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)/rituximab
Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)/rituximab
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine)/rituximab
OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab)
Nivolumab
Nivolumab/rituximab
Pembrolizumab
Pembrolizumab/rituximab

Graft versus Host disease

- Common complication following allogenic transplant
- May see following transplantation of solid organ rich in lymphocytes (e.g., liver)
- Following transfusion of non-irradiated blood
- Systemic disorder occurring when immune cells from transplanted tissue recognize the recipient's body as foreign and attack its cells

Graft versus Host disease

- Acute GVHD
- occurs within first 100 days post-transplant
- Persistent, recurrent, late-onset acute if occurs after first 100 days
- Chronic GVHD
- occurs after first 100 days
- Overlap syndrome has features of both acute and chronic GVHD

Graft versus Host disease

- Interleukin-2 (IL-2) activation and proliferation of T cells
- Activated T-cells and macrophages produce tumor necrosis factor-alpha (TNF-α)
- Interleukin-1 (IL-1) produced by activated immune cells
- Interleukin-6 (IL-6) promotes B-cell activation and differentiation, as well as inflammatory responses.
- Interleukin-12 (IL-12), produced by Antigen Presenting Cells, stimulates the differentiation of naive T cells into Th1 cells
- Interleukin-17 (IL-17) promotes inflammation and tissue damage i particularly in the gut.
- Interferon-gamma (IFN-γ), secreted by activated T-cells
- Transforming growth factor-beta (TGF-β)generally has immunosuppressive properties in GVHD, regulating T-cell differentiation and function.

Graft versus Host disease

- In the gastrointestinal (GI) tract, apoptosis of epithelial cells is the most important feature. Dilated crypts, crypt destruction, villus atrophy, and neutrophilic infiltration can also be observed in small bowel specimens.70%
- A liver biopsy typically shows dysmorphic small bile ducts with portal inflammation. 44%
- Histopathological damage of the skin ranges from minimal vacuolization to separation of the dermis from the epidermis. Grades of skin GVHD are as follows 74%
- Grade I: Minimal vacuolization in the epidermis
- Grade II: Vacuolization and dyskeratotic bodies
- Grade III: Subepidermal cleft formation
- Grade IV: Separation of the dermis from the epidermis

Graft versus Host disease

- Chronic GVHD shares many features with collagen vascular disorders and systemic sclerosis
- In the oral cavity, this condition may present as lichen planus with a risk of developing into oral squamous cell carcinoma, which differs from classical pathology and appears more aggressive in patients with stem cell transplantation
- Recurrent infections can be a cause of death, often complicating immunosuppression
- Ocular involvement indicates poor prognosis in GVHD, usually affecting the ocular surface and manifesting with dry eye or keratoconjunctivitis sicca.
- Grade 1 GVHD is usually managed with topical steroids to control local symptoms. Topical tacrolimus is an option for steroid-resistant disease.
- Grade 2 or higher GVHD requires the addition of systemic steroids, most commonly methylprednisolone. .
- In cases of GI involvement, adding a nonabsorbable corticosteroid (budesonide or beclomethasone) is more effective than systemic treatment alone. Steroids should be avoided if a GI infection is present.
- May require 2-3 years maintenance
- 25% stage 3, 5% stage 4 survival

Graft versus Host disease staging

- Gastrointestinal System
- Stage 1: Diarrhea >500 cc/day
- Stage 2: Diarrhea >1000 cc/day
- Stage 3: Diarrhea >1500 cc/day

Graft versus Host disease staging

- Skin
- Stage 1: Maculopapular rash <25% of the body
- Stage 2: Maculopapular rash 25% to 50% of the body
- Stage 3: Generalized erythroderma
- Stage 4: Generalized erythroderma with bullae
- Liver
- Stage 1: Bilirubin 2 to 3, AST 150 to 750
- Stage 2: Bilirubin 3 to 6
- Stage 3: Bilirubin 6 to 15
- Stage 4: Bilirubin >15

Graft versus Host disease

- GI
- Stage 1: Diarrhea >500 cc/day
- Stage 2: Diarrhea >1000 cc/day
- Stage 3: Diarrhea >1500 cc/day
- Stage 4: Diarrhea >2000 cc/day or severe abdominal pain

Graft versus Host disease

Glucksberg Grade:

- Mild: No liver or GI involvement, stage 1 to 2 skin involvement
- Moderate: Stage 1 liver or GI involvement, stage 1 to 3 skin involvement
- Severe: Stage 2 to 3 skin, liver, or GI involvement
- Life-threatening: stage 2 to 4 liver or GI involvement, stage 1 to 4 skin involvement
- **International Cone Marrow Transplant Registry Severity Index:**
- Mild: No liver or GI involvement, stage 1 skin involvement
- Moderate: Stage 1 to 2 liver or GI involvement, stage 2 skin involvement
- Severe: Stage 3 skin, liver, or GI involvement
- Life-threatening: Stage 4 skin, liver, or GI involvement