Acute Leukemia

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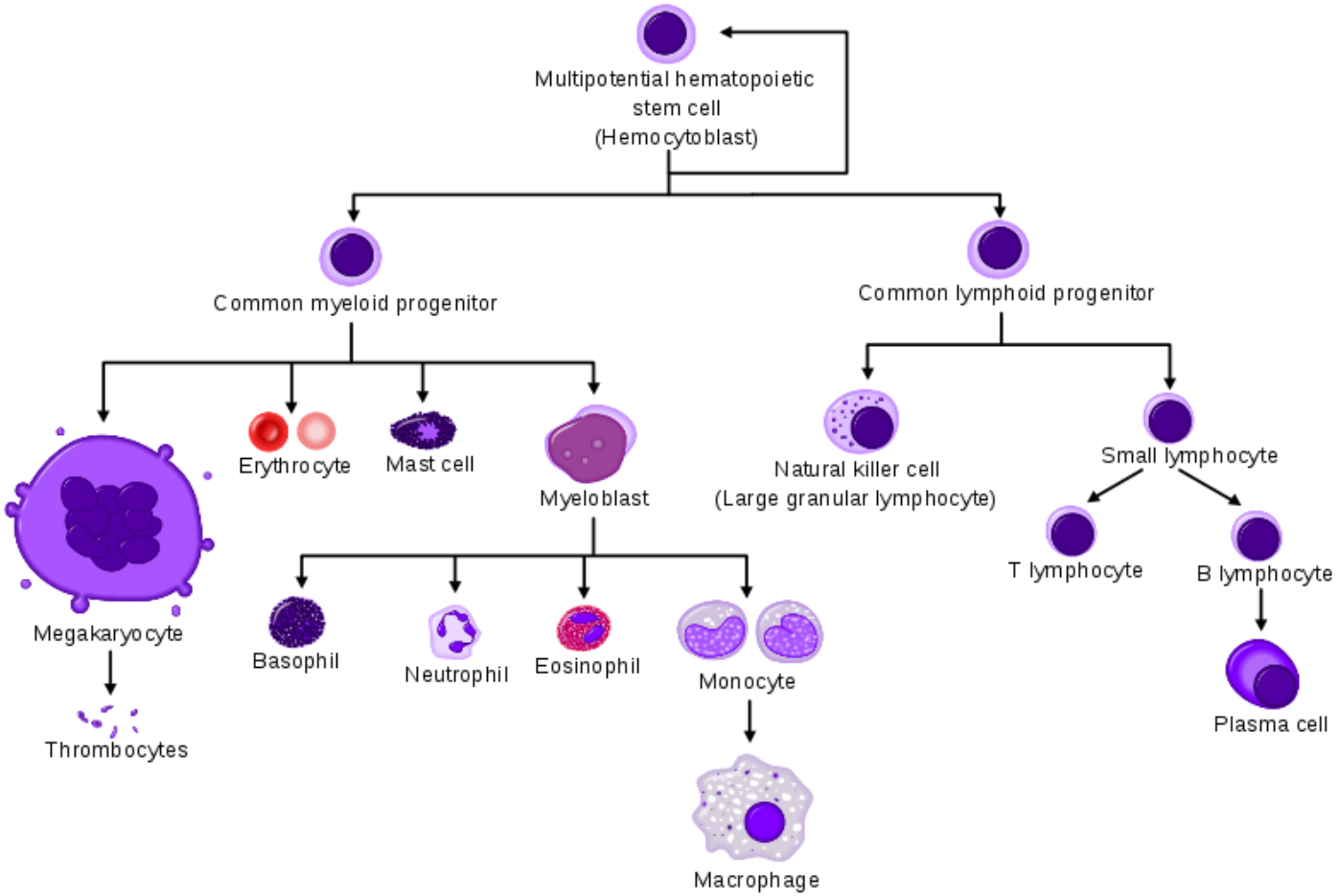
Disclosures

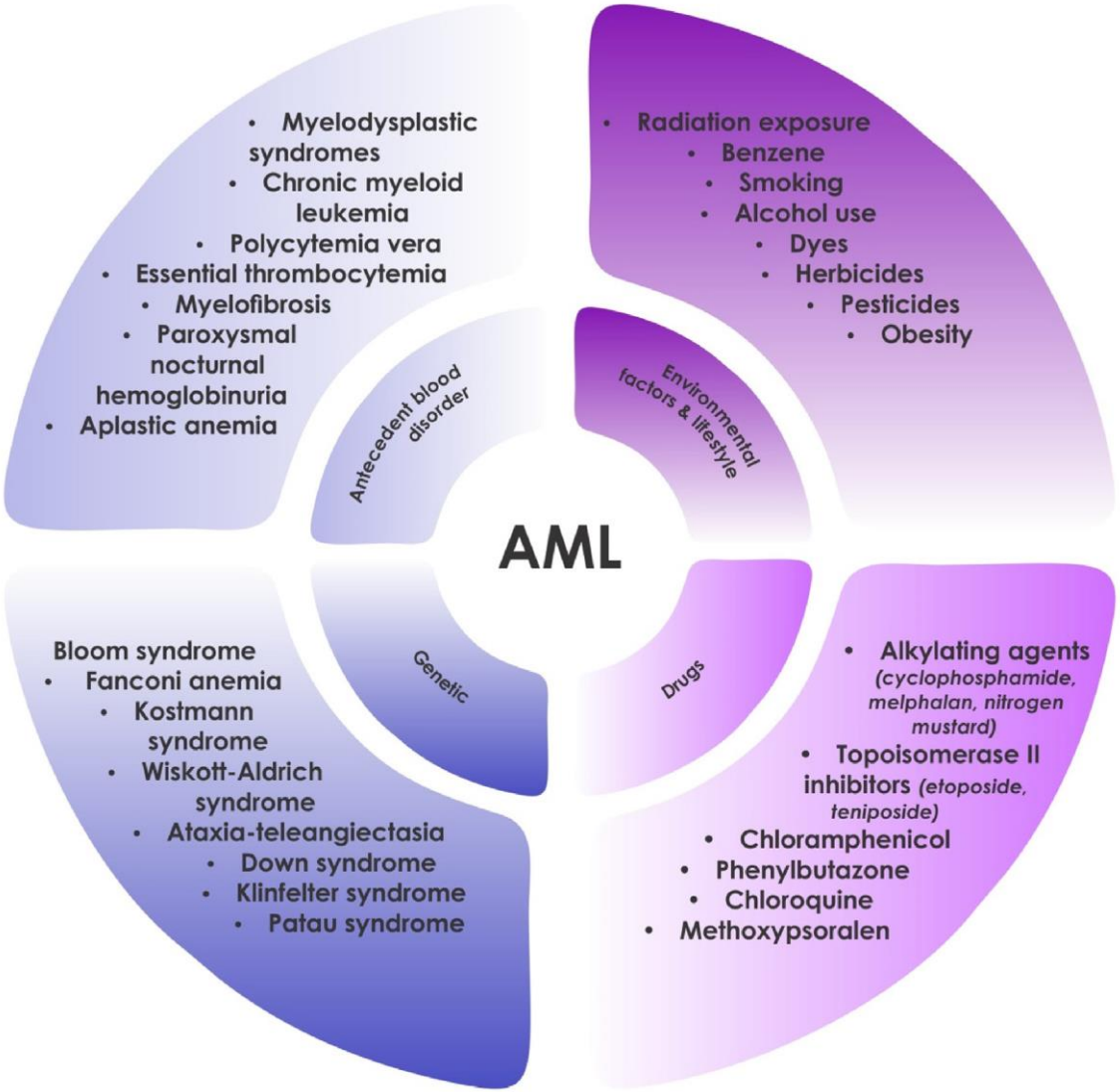
Jazz Pharmaceuticals Speaker Bureau


Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Megakaryocyte
Thrombocytes
Erythrocyte
Mast cell
Myeloblast
Basophil
Neutrophil
Eosinophil
Monocyte
Macrophage
Natural killer cell (Large granular lymphocyte)
Small lymphocyte
T lymphocyte
B lymphocyte
Plasma cell

Acute myeloid leukemia (AML)

- Heterogeneous clonal malignancy in which immature hematopoietic cells proliferate and accumulate in tissues
- Most common acute leukemia in adults
- Median age is 67 years
- Survival remains poor

Predisposing factors of AML



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Presentation

- Constitutional symptoms
- Sings and symptoms of BM infiltration
- Leukocytosis
- Tissue infiltration
- DIC

Classification

A. FAB in 1970s:
   - Based on morphology and cytochemical criteria
   - M0-M7

B. WHO in 2000 & 2008:
   - Incorporate epidemiology, clinical features, biology, immunophenotype & genetics
   - Include multiple groups & subgroups

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Table 1. Myeloid neoplasms with germ line predisposition, AML and related precursor neoplasms, and acute leukemias of ambiguous lineage (WHO 2016)

Myeloid neoplasms with germ line predisposition (see Table 2)	
AML and related neoplasms	**AML and related neoplasms (cont'd)**
AML with recurrent genetic abnormalities	Acute myelomonocytic leukemia
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	Acute monoblastic/monocytic leukemia
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Pure erythroid leukemia#
Acute promyelocytic leukemia with *PML-RARA**	Acute megakaryoblastic leukemia
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*†	Acute basophilic leukemia
AML with t(6;9)(p23;q34.1); *DEK-NUP214*	Acute panmyelosis with myelofibrosis
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*	Myeloid sarcoma
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*‡	Myeloid proliferations related to Down syndrome
Provisional entity: AML with *BCR-ABL1*	Transient abnormal myelopoiesis
AML with mutated *NPM1*§	Myeloid leukemia associated with Down syndrome
AML with biallelic mutations of *CEBPA*§	Blastic plasmacytoid dendritic cell neoplasm
Provisional entity: AML with mutated *RUNX1*	**Acute leukemias of ambiguous lineage**
AML with myelodysplasia-related changes‖	Acute undifferentiated leukemia
Therapy-related myeloid neoplasms¶	MPAL with t(9;22)(q34.1;q11.2); *BCR-ABL1***
AML, NOS	MPAL with t(v;11q23.3); *KMT2A* rearranged
AML with minimal differentiation	MPAL, B/myeloid, NOS
AML without maturation	MPAL, T/myeloid, NOS
AML with maturation	

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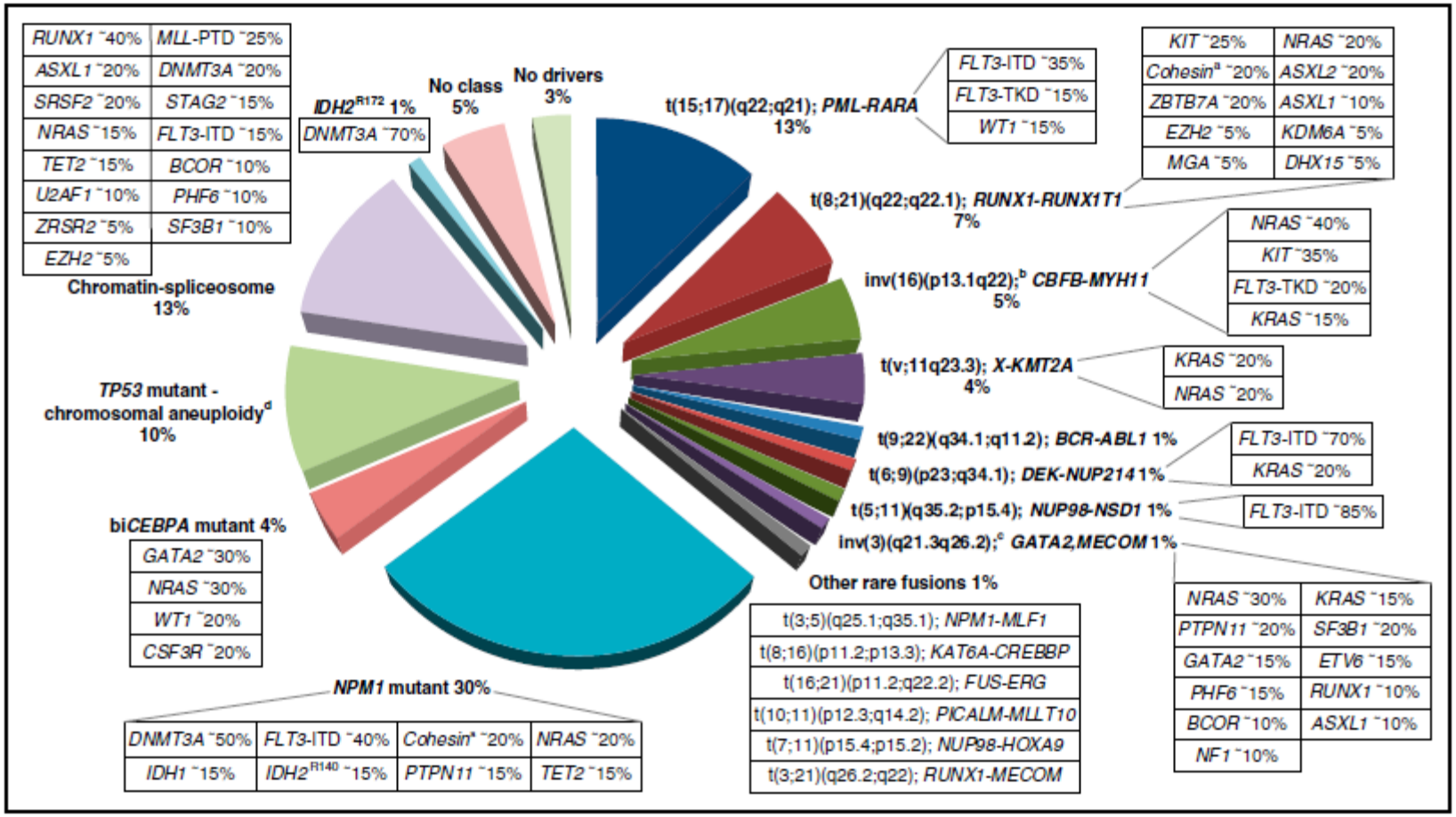
Diagnosis

- ≥20% myeloblasts and/or equivalent in PB or/and BM

- Patients with t(8;21), inv(16), t(16;16), and t(15;17) irrespective of blast count

Risk Stratification

- Clinical features:
  - Advanced age
  - Extramedullary disease
  - History of antecedent hematological disorder
  - WBC# >50,000 at diagnosis
  - Therapy-related
- Cytogenetics
- Molecular markers



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Comparison of the Revised MRC, ELN and SWOG Risk Classification Systems of AML.

Groups	MRC_{2010}	ELN		SWOG
Favorable	t(15;17)(q22;q21) t(8;21)(q22;q22) inv(16)(p13;q22)/t(16;16)(p13;q22)	t(8;21)(q22;q22) (inv(16)/t(16;16)(p12;q22) NPM1+ and FLT3-ITD-WT (NK) Mutated CEBPA (NK)		t(15;17), t(8;21) inv(16)/t(16;16)/del(16q)
Intermediate	Those cytogenetic abn. not classified as favorable or adverse	Int.1	NPM1+ & FLT3-ITD + (NK) NPM1-WT & FLT3-ITD + (NK) NPM1-WT & FLT3-ITD-WT	Normal +8, +6, −Y, del(12p)
		Int.2	t(9;11)(p22;q23) cytogenetic abn. not classified as favorable or adverse	
Adverse	abn(3q)(excluding t(3;5)(q21–25;q31–35], inv(3)/t(3;3)(q21;q26) add(5q), del(5q), −5, −7, add(7q)/del(7q) t(6;11)(q27;q23), t(10;11)(p11–13;q23), t(11q23)[excl. t(9;11) (p21–22;q23) and t(11;19)(q23;p13)], t(9;22)(q34;q11) -17/abn(17p) complex (≥4 unrelated abnormalities)	Inv(3)/t(3;3)(q21;q23) t(6;9)(p23;q34) t(v;11)(v;23), MLL rearranged -5 or del(5q) -7 Abn(17p) complex (≥3 unrelated abnormalities)		abn(3q) del(5q)/-5, -7/del(7q) t(6;9), t(9;22), 9q, 11q, 20q, 21q 17p complex (≥3 unrelated abnormalities)

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Treatment

- **Induction**
  - "7+3" regimen
    - The regimen was introduced over 4 decades ago
    - Remains the standard of care at the current time
- **Post-remission**
  - Age-adjusted high-dose cytarabine x 3-4 vs. allogeneic HSCT
    - Based on risk stratification, donor availability and patient eligibility
- **Relapse/refractory**
  - Carry very poor prognosis
  - Allogeneic HSCT if possible after achieving CR with salvage chemotherapy
  - Salvage treatment with FLAG, MCE, hypomyethylating agents and supportive care
  - Clinical trials!!

Table 10. Novel therapies in clinical development in AML

Novel therapies in clinical development	
Protein kinase inhibitors	• FLT3 inhibitors (midostaurin, quizartinib, gilteritinib, crenolanib) • KIT inhibitors • PI3K/AKT/mTOR inhibitors • Aurora and polo-like kinase inhibitors, CDK4/6 inhibitors, CHK1, WEE1, and MPS1 inhibitors • SRC and HCK inhibitors
Epigenetic modulators	• New DNA methyltransferase inhibitors (SGI-110) • HDAC inhibitors • IDH1 and IDH2 inhibitors • DOT1L inhibitors • BET-bromodomain inhibitors
Chemotherapeutic agents	• CPX-351 • Vosaroxin • Nucleoside analogs
Mitochondrial inhibitors	• Bcl-2, Bcl-xL, and Mcl-1 inhibitors • Caseinolytic protease inhibitors
Therapies targeting oncogenic proteins	• Fusion transcripts targeting • EVI1 targeting • NPM1 targeting • Hedgehog inhibitors
Antibodies and immunotherapies	• Monoclonal antibodies against CD33, CD44, CD47, CD123, CLEC12A • Immunoconjugates (eg, GO, SGN33A) • BiTEs and DARTs • CAR T cells or genetically engineered TCR T cells • Immune checkpoint inhibitors (PD-1/PD-L1, CTLA-4) • Anti-KIR antibody • Vaccines (eg, WT1)
Therapies targeting AML environment	• CXCR4 and CXCL12 antagonists • Antiangiogenic therapies

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A. **Anthracycline-** cardiotoxicity, BM suppression, extravasation, and secondary leukemia

B. **Cytarabine-** BM suppression, neurotoxicity, chemical conjunctivitis, rash and fever

C. **Hypomethylating agents**- well-tolerated, pancytopenia, constipation

Neutropenic fever

- Defined as single temperature of > 38.3C (101F) or a temperature >38.0C (100.4F) sustained for >1 hour, in patient with neutropenia (ANC <500)
  - An infectious source is identified in 20-30%
    - 80% of identified infections arise from patient endogenous flora
    - There is shift with more gram-positive infections due to increased use of indwelling catheters
  - Gram-negative bacteria carries more risks and should be covered

- Empiric therapy should be started promptly
- Initial therapy include one of those options:
  - Zosyn, Meropenem, Cefepime, Ceftazidime
  - PCN-allergy: Aztreonam + vancomycin
- Hemodynmic instability/soft-tissue infection- we add vancomycin

Tumor lysis syndrome

- Occurs shortly after initiating therapy or even spontaneously in aggressive malignancies
- Diagnosed by combination of electrolytes imbalanced
  - Hyperurecemia
  - Hyperkalemia
  - Hyperphosphatemia
  - Hypercalcemia
- TLS can results in ARF, cardiac arrhythmia, N/V, anorexia, lethargy, muscle cramps, tetany
- Prevention is essential
  - Combination of IVF + allopurinol
- Treatment
  - Rasburicase- urate oxidase which promotes degradation or uric acid
  - HD
  - Management of electrolytes imbalance

Supportive care

Infectious disease prophylaxis

- There is a debate on the importance of antibacterial prophylaxis during induction therapy in acute leukemia
- Randomized study documented benefit of anti-mold prophylaxis during induction in AML
- Pts are usually given prophylaxis anti-VZV during treatment

Supportive transfusion

- **Single donor**, **irradiated** and **leuko-depleted** transfusion

Acute promyelocytic leukemia

- Subtype of AML (M3) with distinctive biological and clinical features
  - Accounts for 10-15% of AML cases
  - Higher incidence in Hispanics
- Highly curable, without chemotherapy in low/Int-risk
- Balanced reciprocal t(15;17)
  - Generates fusion transcript joining PML and RAR-α
- Unique susceptibility of differentiating upon exposure to ATRA
  - Differentiation/apoptosis when exposed to ATO
- Standard treatment is a combination with ATRA and ATO, +/- chemotherapy

- **Significant risk for DIC on presentation**
  - Start ATRA on first suspicion of APL
  - BID-TID CBC and fibrinogen check
    - plt transfusion to keep # >50k
    - Cryoprescipitate to keep fibrinogen >150
- **ATRA "differentiation" syndrome**
  - SOB, fever, chest pain, leukocytosis and b/l infiltrate on CXR
  - Can be fatal
  - Steroid, consider holding ATRA/ATO when severe
- **QTc prolongation with ATO**
  - Weekly EKG
  - Keep K >4.0, Mg >2, avoid medications prolong QTc
- **ATRA induced pseudotumor cerebri**

Acute lymphoblastic leukemia

- Uncommon leukemia in adults
  - ~10-20%
- Bimodal distribution;
  - 4-10 and at age 50

- Outcomes have improved significantly in children with ALL, but not in adults
  - CR; 100% vs. 65%-90%
  - 5-yr survival; ~90% vs. 25-50%

Presentation

- Non-specific constitutional symptoms, symptoms related to cytopenias, bone pain, splenomegly and LAP
- Mediastinal mass is common in T-cell
- Extramedullary involvement; CNS, testis, skin etc
- Always needs CNS evaluation at diagnosis

B-cell:

- 70-85% of ALL cases
- + CD19, CD79a, TdT and HLA-DR
- Burkitt's leukemia/lymphoma is classified as mature B-lymphoid neoplasm

T-cell:

- 15-25% of ALL cases
- + TdT, CD7, CD3, co-expressed CD4 and CD8
- Early thymic T cell is a distinct subtype
  - associated with dismal outcomes

Risk Stratification

A. Clinical:
   - Age
   - Elevated wbc#
   - Failure to achieve early CR, MRD
B. Cytogenetics:
   - Philadelphia chromosome/ Ph-like
   - Complex cytogenetics (>5 abn)
   - MLL mutation
   - Ploidy status
C. Molecular:
   - CRLF2, IKROS, NOTCH, HOX11, etc

CNS involvement

- Uncommon at dx
- High CNS relapse if no CNS-directed prophylactic therapy is provided
- CSI is effective
  - Carries significant risk of late toxicities
- Systemic chemotherapy alone is usually inadequate
  - Difficult to maintain therapeutic concentrations of drugs in CSF
- IT & systematic chemotherapy emerged as most effective approach to prevent CNS relapse
  - CNS relapse ~1-3%

Treatment

- The introduction of intensive and prolong mutli-agent chemotherapy changed the natural history of ALL in pediatrics
- BFM regimen is widely used, tested initially in pediatrics, and then tested in modified fashion in adults
- Most modern ALL regimens include
  - Induction-anthracycline, vincristine, steroids, +/-cytoxan & ASP
  - Post-remission consolidation- 6-8 cycles
  - Maintenance therapy- 2-3 years
- No consensus of the optimal regimen in adults yet
- Allogeneic HCT remains recommended for high-risk and relapsed cases

Study	Year	Pt#	CR%	LFS	OS
SWOG 8417/8419	2001	353	62	25%, 5 yrs	35%, 8 yrs
NILG 08/96	2001	121	84	48%, 3 yrs	49%, 3 yrs
JALSG 93	2002	263	78	30%, 6 yrs	30%, 6 yrs
Sweden	2002	153	86	30%, 5 yrs	28%, 5 yrs
GIMEMA 02/88	2002	767	82	33%, 9 yrs	27%, 9 yrs
MDACC	2004	288	92	38%, 5 yrs	38%, 5 yrs
EORTC ALL3	2004	340	74	36%, 6 yrs	36%, 6 yrs
LALA 94	2004	922	84	30%, 5 yrs	36%, 5 yrs
GOELAL 02	2004	198	86	NR	41%, 6 yrs
PETHEMA ALL93	2005	222	82	35%, 5yrs	34%, 5 yrs
GMALL 07	2007	713	89	NR	54%, 5 yrs
MRC-ECOG	2008	1646	90	NR	39%, 5 yrs
HOVON	2009	433	67	NR	37%, 5 yrs

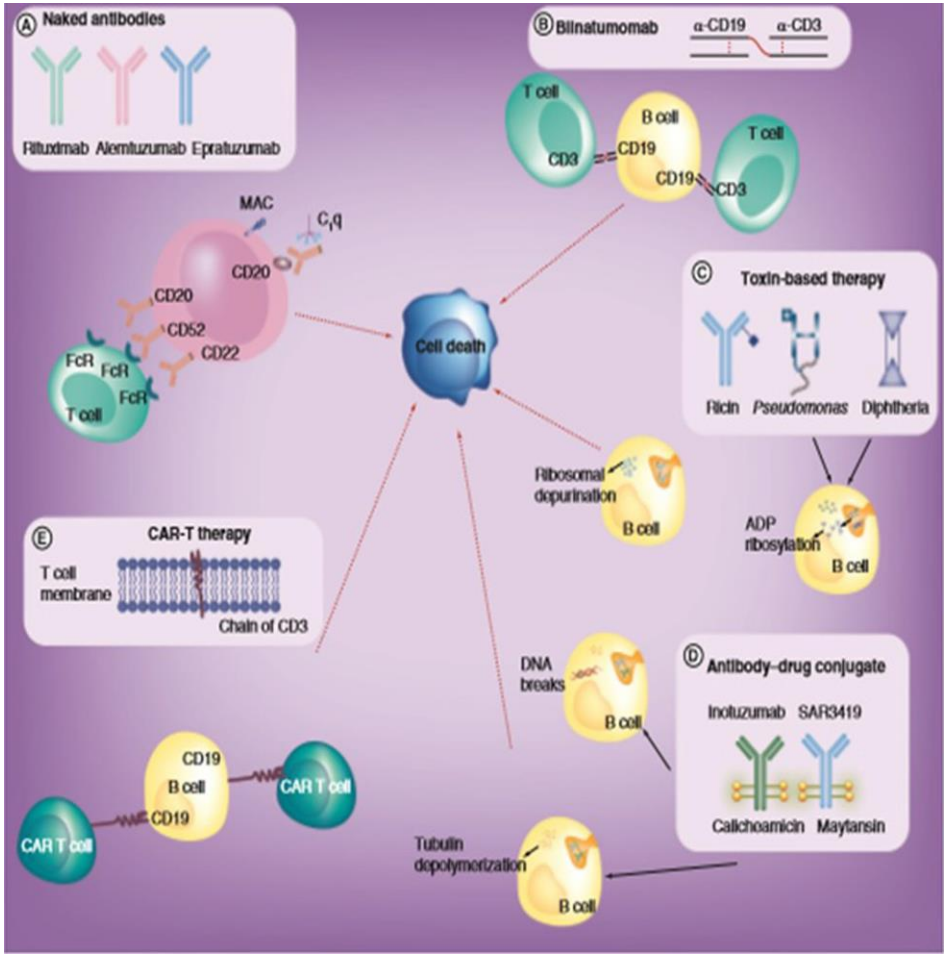
ALL drug toxicities

- **Anthracycline**- cardiotoxicity, BM myelosuppression, secondary leukemia
- **Vincrisitine**- neuropathy, ileus
- **MTX**- hepatotoxicity, nephrotoxicity, mucosititis, pneumonitis
- **Asparaginase-** hepatotoxicity, pancreatitis, neurotoxicity, coagulopathy, thrombosis, allergic reactions
- **Alkylating agents-** myelosuppression, secondary MDS/AML
- **Intrathecal chemotherapy-** headaches due to CSF leak, arachnoiditis, N/V when given through Ommaya reservoir
- **Cranial irradiation-** secondary cancer, cognitive impairment

Ph+ ALL

- Ph-chromosome incidence increases with age
  - ~30-50% of adult ALL
- Historically, Ph+ ALL used to carry poor prognosis,
  - Low CR rate & short duration of remission
  - Only cure was alloHCT
- The introduction of TKIs transformed the disease
  - Higher deep remissions
  - More pts able to proceed with alloHCT
  - Improved OS
- TKI therapy is well-tolerated and the majority of Ph+ ALL achieves CR nowadays with mild therapy

- **TKIs toxicities:** myelosuppression, QTc prolongation, dasatinib-pleural effusion, colitis


A Naked antibodies
Rituximab Alemtuzumab Epratuzumab
B Blinatumomab
α-CD19
α-CD3
T cell
B cell
CD3
CD19
CD19
CD3
T cell
MAC
C1q
CD20
CD20
CD52
CD22
FcR
FcR
FcR
T cell
Cell death
C Toxin-based therapy
Ricin
Pseudomonas
Diphtheria
Ribosomal depurination
B cell
ADP ribosylation
B cell
E CAR-T therapy
T cell membrane
Chain of CD3
DNA breaks
B cell
D Antibody–drug conjugate
Inotuzumab
SAR3419
Calicheamicin
Maytansin
CD19
B cell
CD19
CAR T cell
CAR T cell
Tubulin depolymerization
B cell

Cytokine-release syndrome

- New effective immunotherapies have been approved/tested in ALL
  - BiTE antibody
  - CAR T cells therapy

- There is risk of cytokine-release syndrome with immunetherapy
  - Manifestations: Fever, chills, hypotension, SOB, neurological manifestations
  - It's the result of rapid immune reaction driven by the massive release of large amount of cytokines, IL-6, INF, etc
  - Consensus algorithm was proposed

- Treatment include: aggressive supportive care, IL-6 monoclonal antibody, and steroid in severe cases