Leukemia: Types and Updates in Treatment

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Objectives

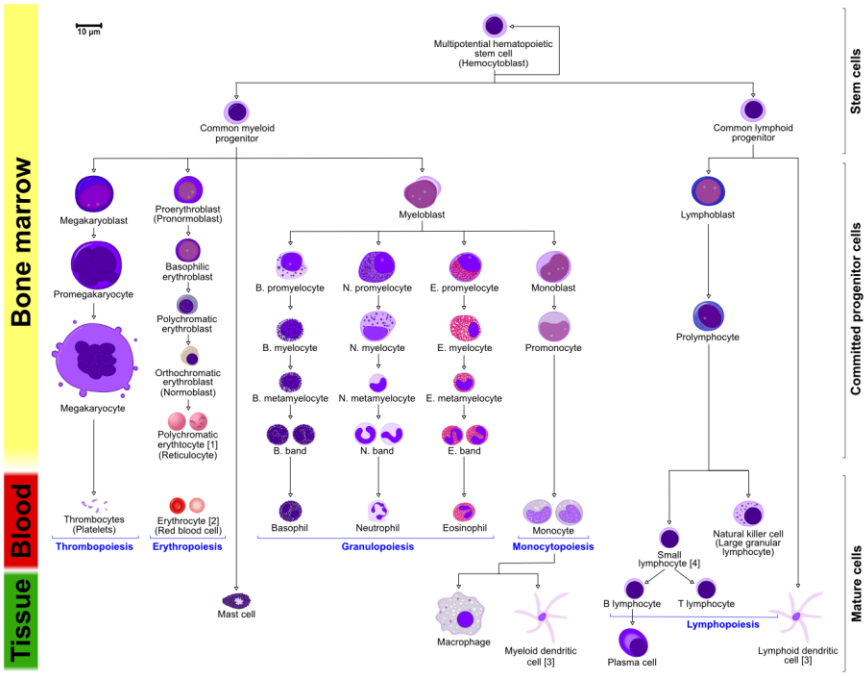
- Identify signs and symptoms of leukemia
- Differentiate acute leukemias vs chronic leukemias and subtypes
- Assess basic blood tests to help assess type of leukemia
- Learn about leukemia treatments

Background

- **White blood cells (WBCs)** include several different types. Each has its own role in protecting the body from infections. The three major types are neutrophils, lymphocytes, and monocytes.
  - Neutrophils (also known as granulocytes or polys) destroy most bacteria.
  - Lymphocytes are responsible for destroying viruses and for overall management of the immune system. When lymphocytes see foreign material, they increase the body's resistance to infection.
  - Monocytes destroy germs such as tuberculosis.
  - When WBC is low (specifically neutrophil subtype) risk of infections and infectious complications is increased

Background

- **Red blood cells (RBCs)**: The percentage of RBCs in the blood is called hematocrit. The part of the RBC that carries oxygen is a protein called hemoglobin. When the bone marrow is working normally, the RBC count or hemoglobin remains stable.
- **Platelets** are the cells that help control bleeding. When you cut yourself, the platelets collect at the site of the injury and form a plug/clot to stop the bleeding.
- **Bone marrow** is the tissue within the bones where blood cells are made. The bone marrow is made up of blood cells at different stages of maturity. All blood cells begin in the bone marrow as stem cells. Stem cells are very immature cells. When there is a need, the stem cells are signaled to develop into mature WBCs, RBCs, or platelets.



Hematopoiesis

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Normal blood vs leukemia blood

Adult normal ranges:

Parameter		Male	Female
Haemoglobin	g/L	135 - 180	115 - 160
WBC	$x10^9/L$	4.00 - 11.00	4.00 - 11.00
Platelets	$x10^9/L$	150 - 400	150 - 400
MCV	fL	78 - 100	78 - 100
PCV		0.40 - 0.52	0.37 - 0.47
RBC	$x10^{12}/L$	4.5 - 6.5	3.8 - 5.8
MCH	pg	27.0 - 32.0	27.0 - 32.0
MCHC	g/L	310 - 370	310 - 370
RDW		11.5 - 15.0	11.5 - 15.0
Neutrophils		2.0 - 7.5	2.0 - 7.5
Lymphocytes		1.0 - 4.5	1.0 - 4.5
Monocytes		0.2 - 0.8	0.2 - 0.8
Eosinophils		0.04 - 0.40	0.04 - 0.40
Basophils		< 0.1	< 0.1

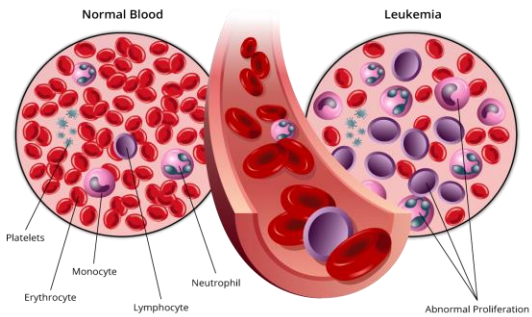

image: https://www.advanceayurveda.in/wp-content/uploads/2018/10/Leukemia-Diagram.png

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Leukemia Signs/Symptoms

- Fatigue, weight loss, loss of appetite, drenching night sweats, fevers, infection, abnormal bleeding/bruising, SOB
- CBC can show high or low WBCs, anemia, thrombocytopenia
- Enlarged spleen, enlarged lymph nodes, swollen gums, rash (leukemia cutis)

Different types of leukemia

- Acute lymphocytic leukemia (**ALL**) – most common form of leukemia in children
- Acute myelogenous leukemia (**AML**) – most common form of acute leukemia overall, affecting both adults and children
- Chronic lymphocytic leukemia (**CLL**) – most prevalent form of chronic leukemia in adults
- Chronic myelogenous leukemia (**CML**) – Mainly affects adults and may produce few or no symptoms for months or even years. +BCR-ABL.

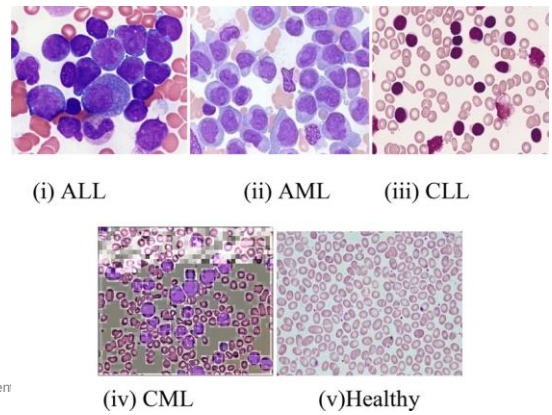

Image: https://www.researchgate.net/publication/353956889/figure/fig3/AS:1058023229382656@1629263803013/Different types-of-Leukemia-i-Acute-Lymphocytic-Leukemia-ii-Acute-Myelogenous.png

Characteristics of major subtypes

	Type of Leukemia			
Factor	**ALL**	**AML**	**CLL**	**CML**
Age	Children (75%)	Adults (85%)	Over 40 years	30-50 years
Prognosis	Very good	Poor	Good	Poor
Survival, mean	—	2 years	Stage I (19 months) Stage IV (12 years)	3-4 years —
Remissions	90%	60-80%	—	—
Duration	Usually long term	9-24 months	—	—
Cures	50-70%	10-30%	—	
	ALL	**AML**	**CLL**	**CML**
Age	Adults (25%)	Children (15%)	Children (rare)	Children (rare)
Prognosis	Poor	Poor	—	—
Survival, mean	26 months	—	—	—
Remissions	50-70%	56-66%	—	—
Duration	10-19 months	8-12 months	—	—
Cures	20%	20-40%	—	

ALL, Acute lymphocytic leukemia; *AML*, Acute myelogenous leukemia; *CLL*, Chronic lymphocytic leukemia; *CML*, Chronic myelogenous leukemia.
Data from Wetzler M, Byrd JC, Bloomfield CD: Acute and chronic myeloid leukemia. In Kasper DL, et al, editors: Harrison's principles of internal medicine, *ed 16, New York, 2005, McGraw-Hill; and Armitage JO, Longo DL: Malignancies of lymphoid cells. In Kasper DL, et al, editors:* Harrison's principles of internal medicine, *ed 16, New York, 2005, McGraw-Hill.*

Staging in leukemia

- Stage is location/ how advanced within body
- Acute leukemia and CML does not have "staging", only "risk groups"
- CLL is staged. Rai system is used most commonly for CLL staging
  - Stage 0 – high levels of white blood cells (**lymphocytosis**) only
  - Stage 1 – high levels of white blood cells + enlarged lymph nodes (**lymphadenopathy**)
  - Stage 2 – + enlarged spleen (**splenomegaly**)
  - Stage 3 – + **Anemia** (low red blood cells)
  - Stage 4 – + **Thrombocytopenia** (low platelet cells)

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ACUTE leukemia (AML, ALL)

- Immature cells, “blast cells”
- Condition progresses very rapidly, creating a large number of abnormal white blood cells that do not function or mature properly
- Symptoms tend to appear earlier and be more severe than the symptoms of chronic leukemia

Acute leukemia classification

- Modern classifications (WHO & European LeukemiaNet) based on chromosome and molecular alterations
  - Risk groups
  - ALL: assess if has Philadelphia chromosome t(9;22), BCR-ABL
  - APL (acute promyelocytic leukemia) classified separately
- Older classifications were based on cell type or morphology

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AML Classification (non-APL)

Risk Category[*,†]	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*[†,‡] inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*[†,‡] Mutated *NPM1*[†,§] without *FLT3*-ITD bZIP in-frame mutated *CEBPA*[‖]
Intermediate	Mutated *NPM1*[†,§] with *FLT3*-ITD Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[†,¶] Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* t(v;11q23.3)/*KMT2A*-rearranged[#] t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)* t(3q26.2;v)/*MECOM(EVI1)*-rearranged -5 or del(5q); -7; -17/abn(17p) Complex karyotype,[**] monosomal karyotype[††] Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*[‡‡] Mutated *TP53*[a]

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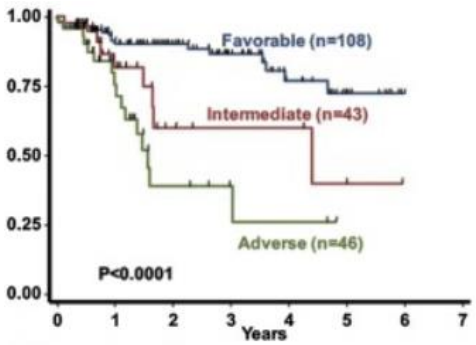
Acute leukemia prognosis

- Prognostic factors include:
  - Age
  - Performance status
  - Cytogenetic and molecular findings (risk groups)
  - History of prior chemotherapy/radiation
  - History of prior MDS or other hematologic disorders (for AML)
- Long-term survival has improved in younger population, more recently also modest improvement in older patients (age >60-65)
  - Long-term survival/cure in ~40% of younger adults, worse in older patients



Leuk Res. 2018;66:20-27.

Chronic leukemia (CLL, CML)

- Overproduction of a more mature cell type. Inhibits the development of blood stem cells, ultimately causing them to function less effectively than healthy mature blood cells
- Tends to be less severe and progresses more slowly than acute leukemia
- As the cancer progresses and spreads, symptoms may appear
- CML has characteristic chromosomal alteration: Philadelphia chromosome t(9;22), BCR-ABL

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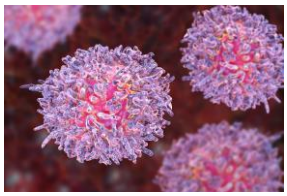
Rare types of leukemia

- **Hairy cell leukemia -** bone marrow makes too many lymphocytes (type of white blood cell)



- **Myeloproliferative neoplasms** - a group of slow-growing blood cancers in which the bone marrow makes too many abnormal red blood cells, white blood cells, or platelets

CHRONIC MYELOPROLIFERATIVE DISORDERS

DISEASE	MOLECULAR DEFECT
Chronic myelogenous leukemia	BCR-ABL
Chronic eosinophilic leukemia	FIP1L1-PDGFRA
Chronic neutrophilic leukemia	BCR-ABL p230
Chronic myelomonocytic leukemia	TEL-PDGFRB
Systemic mastocytosis	KIT D8116V
Polycythemia vera	JAK2 V617F (≈90% positive)
Essential thrombocytosis	JAK2 V617F (≈50% positive) MLP W515L/K (≈3% positive) MLP K39N
Primary myelofibrosis	JAK2 V617F (≈50%) MLP W515L/K (≈14%)

- **Myelodysplastic syndrome (MDS)** - a group of diseases in which the bone marrow does not produce enough healthy blood cells, issue with maturing. Can progress to acute leukemia.

Testing in leukemia

Table 2. Common Laboratory Tests for the Evaluation of Leukemia

Test	*Description*	*Clinical applications*
Bone marrow aspirate or biopsy	Examination of a greater concentration of hematopoietic cells	Identification of blast cells in acute myelogenous leukemia and acute lymphoblastic leukemia Extent of marrow involvement correlates with prognosis in chronic lymphocytic leukemia
Cytogenetic testing	Examination of whole chromosomes through karyotyping or fluorescence in situ hybridization analysis	Detection of the Philadelphia chromosome (*BCR-ABL1* fusion gene) for the diagnosis of chronic myelogenous leukemia Identifying chromosomal abnormalities to diagnose leukemia subtypes Can be used to guide treatment and determine prognosis
Flow cytometry with immunophenotyping	Sorting and counting cells (from peripheral blood or bone marrow sample) by specific cell surface markers	Counting cloned cells of lymphoid lineage for the diagnosis of chronic lymphocytic leukemia Identifying certain cell surface markers to diagnose leukemia subtypes
Molecular testing	Testing for specific mutations at the DNA level through polymerase chain reaction testing	Detection of the Philadelphia chromosome (*BCR-ABL1* fusion gene) for the diagnosis of chronic myelogenous leukemia Aids in the diagnosis of leukemia subtypes; can also be used to guide treatment and determine prognosis
Peripheral smear	Examination of whole blood specimen under the microscope	Identification of Auer rods in acute myelogenous leukemia, and blast cells in acute myelogenous leukemia and acute lymphoblastic leukemia

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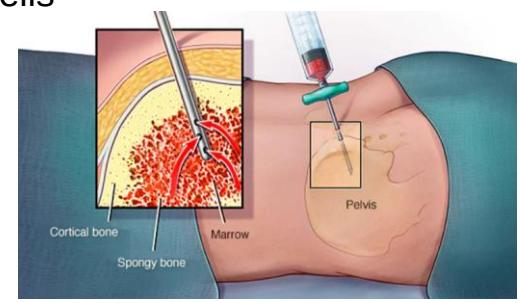
Testing in leukemia

- Imaging with X-ray, CT, or PET scan – can sometimes reveal enlarged lymph nodes, masses, or signs of infection
- Lumbar puncture (spinal tap) – A sample of the cerebrospinal fluid, which fills the spaces around the brain and spinal cord, can be tested for presence of leukemia cells
- Bone marrow aspiration and biopsy A sample of tissue obtained from the hip bone can be tested for the existence of leukemia cells in the bone marrow



Diagnostic technique

Blood cancer sub-type	Diagnostic technique
Acute myeloid leukemia	Immunophenotyping, cytogenetics, molecular testing, Analysis of FLT3, NPM1, and CEBPA, Analysis of PML-RARA
Chronic myelogenous leukemia	Cytogenetics, by FISH, or by PCR targeted at the BCR/ABL fusion gene.
Acute lymphoblastic leukemia	Immunophenotyping, bone marrow examination
Chronic lymphocytic leukemia	smears of the peripheral blood and bone marrow, immunophenotyping, ZAP-70 analysis, and (IgV_H) gene mutation status
Polycythemia vera	Molecular testing on a peripheral blood or bone marrow sample for JAK2 V617F mutation
Essential thrombocythemia	Molecular testing on a peripheral blood or bone marrow sample for JAK2 V617F mutation
Primary myelofibrosis	Molecular testing on a peripheral blood or bone marrow sample for JAK2 V617F mutation
Myelodysplastic syndromes	cellularity, immunophenotyping, cytogenetics, and molecular studies

Staging helps understand the exact type, location, and spread of the cancer and it usually goes hand in hand with diagnosis. However, there are different advanced techniques for the detection of sub-types of blood

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General treatments of leukemia

- Treatment for leukemia varies based on its type and specific characteristics
- Early and accurate diagnosis is essential to achieve the best possible outcome and quality of life

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Acute Leukemia treatments

- Acute leukemia (AML and ALL)
  - Younger and fit (certainly age <60, possibly 61-low 70s)
    - Curative intent
    - Intensive induction chemotherapy followed by consolidation chemotherapy +/- stem cell transplant; prolonged maintenance therapy in ALL
      - ALL: depends if +Ph (Philadelphia chromosome), which includes TKI (tyrosine kinase inhibitor pill)
  - Older or unfit
    - Palliative treatment (not curative intent) vs. supportive care/hospice
    - AML: Hypomethylating agent (azacitidine or decitabine) + venetoclax; other targeted pill therapy to specific mutations
    - ALL: less intensive chemotherapy, steroids alone, or if Ph+ ALL then TKI without as intensive chemotherapy

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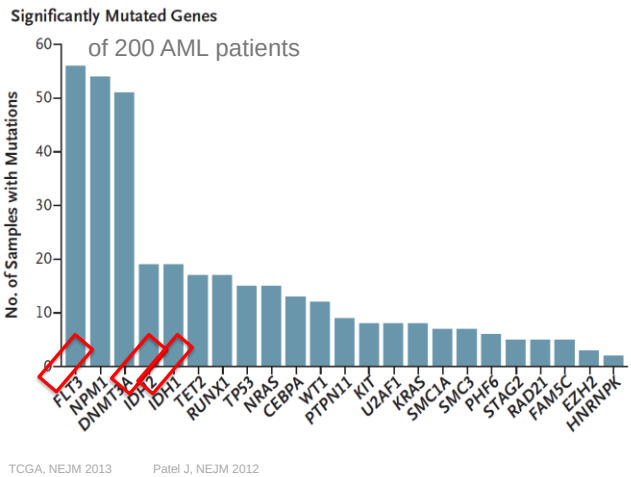
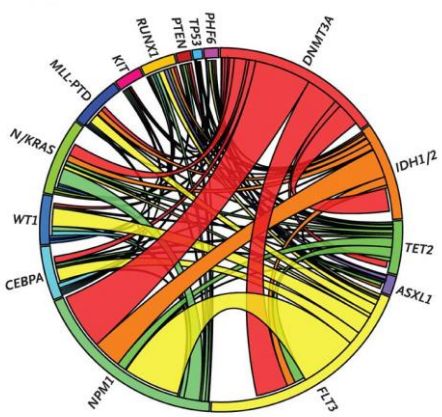
ACUTE MYELOID LEUKEMIA (AML): MUTATIONS



TCGA, NEJM 2013 Patel J, NEJM 2012



AML Specific mutation targeted medications

- Oral options = time away from clinic/infusion
- FLT3 mutation
  - Frontline: Midostaurin or Quizartinib + chemotherapy
  - Second line: Gilteritinib
- IDH1 mutation
  - Ivosidenib or olutasidenib
- IDH2 mutation
  - Enasidenib

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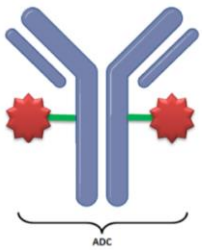
ALL Recent treatment advancements

- Inotuzumab ozogamicin (R/R B-ALL)



- CAR-T cells
  - Tisagenlecleucel or brexucabtagene autoleucel (relapsed/refractory B-ALL)
- Blinatumomab (for detectable minimal residual disease in B-ALL, or relapsed/refractory B-ALL)

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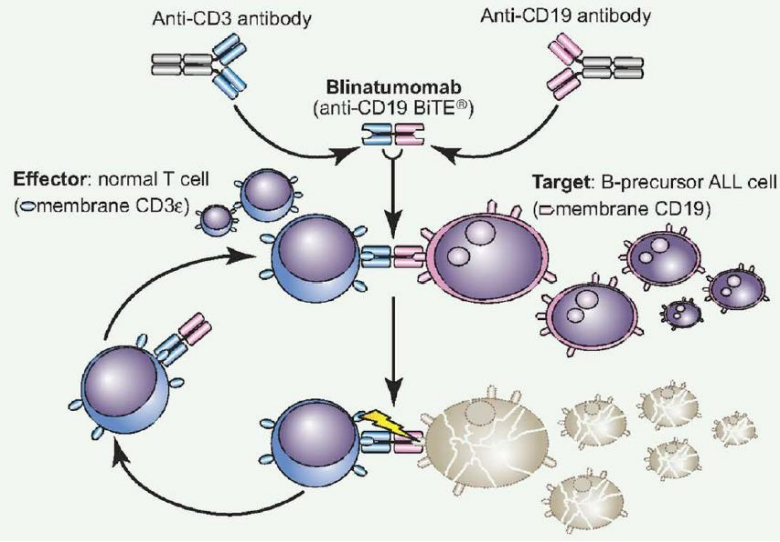
Blinatumomab = CD3-CD19 BiTE (Bispecific T-Cell Engager)



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Chronic leukemia treatments

- CLL
  - Treatment initiated only when indication for treatment
  - BTK inhibitor (Ibrutinib or Acalabrutinib or Zanubrutinib) +/- anti-CD20 mAb
  - Venetoclax + anti-CD20 mAb
- CML
  - Treated with targeted tyrosine kinase inhibitor pills (not traditional chemotherapy)
  - Life-long treatment had been the standard
  - TKI discontinuation (treatment free relapse) now considered if:
    - Chronic phase CML
    - Taking TKI therapy at least 3 years
    - Complete molecular response (undetectable) at least 2 years
    - Close monitoring after discontinuation (monthly testing)
  - Asciminib (approved 10/2021)

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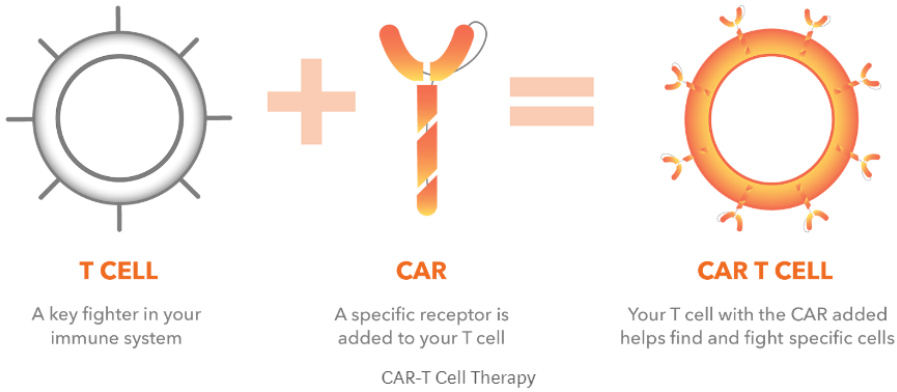
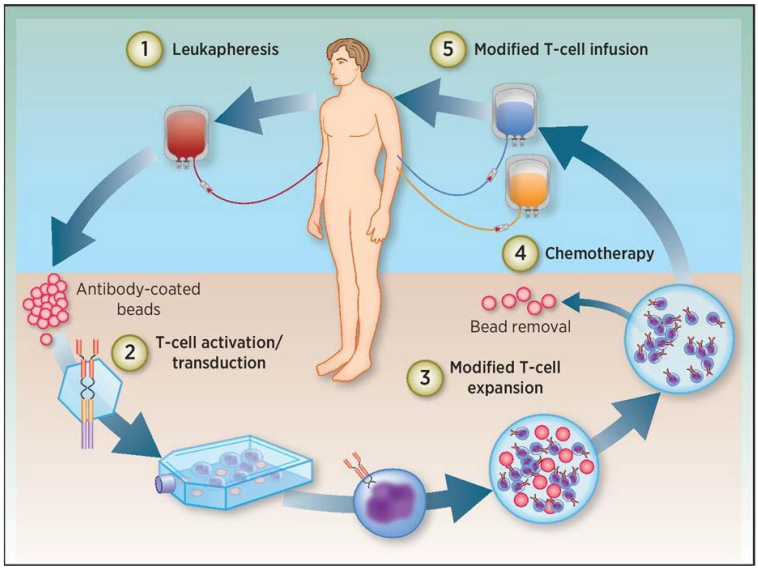
CAR-T cells

- What are they?
  - Chimeric antigen receptor T cells
  - Your own immune cells engineered to target cancer cells with a certain marker



CAR-T cells



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CAR-T cells

- Notable side effects: cytokine release syndrome, neurotoxicity
- Applicability depends on the target (i.e. CD19)
- FDA approved indications in leukemia:
  - B-Acute lymphoblastic leukemia (2nd line or later)
  - Other FDA approved indications in lymphoma and multiple myeloma

Stem Cell Transplant: What is HSCT?

- Replacement of recipient's bone marrow stem cells with either
  - Their own bone marrow stem cells (**autologous**)
  - From a donor (**allogeneic**)
- Frist stem cells are collected from the donor (self if autologous)
  - "BMT" used interchangeably with "SCT"
  - Vast majority of cases collect stem cells from blood (not bone marrow)
    - "Mobilization" with growth factors and collection by apheresis
  - Only rarely are donors collected via bone marrow aspirations

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Autologous Process

1) Mobilization
2) Collection
3) Processing
4) Conditioning treatment
5) Reinfusion

Treatment benefit is the chemotherapy/RT conditioning,

Transplant = “stem cell rescue”

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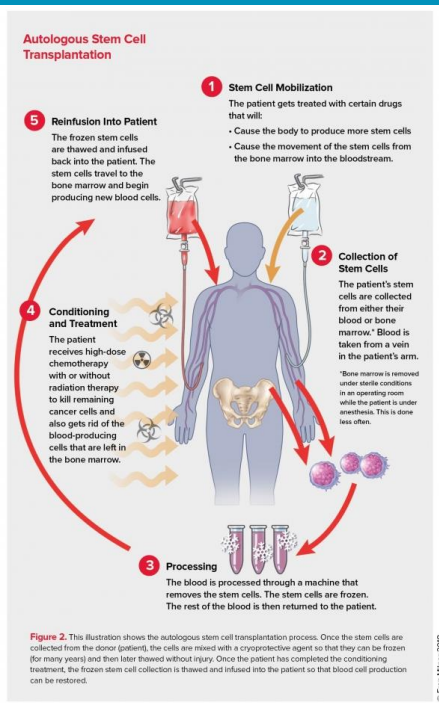

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Allogeneic Process

1) (Mobilization) -> Collection (donor)
2) Processing
3) Conditioning treatment
4) Infusion

Treatment benefit is the conditioning + graft vs. tumor

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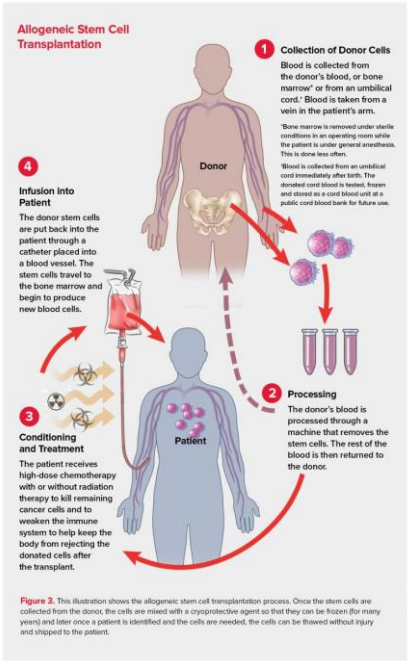

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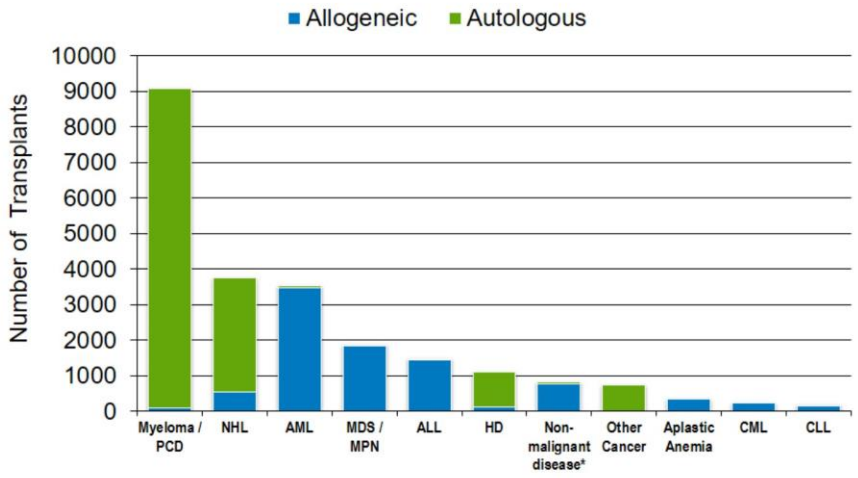
Indications for Hematopoietic Cell Transplant in the US, 2018



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*excludes aplastic anemia.

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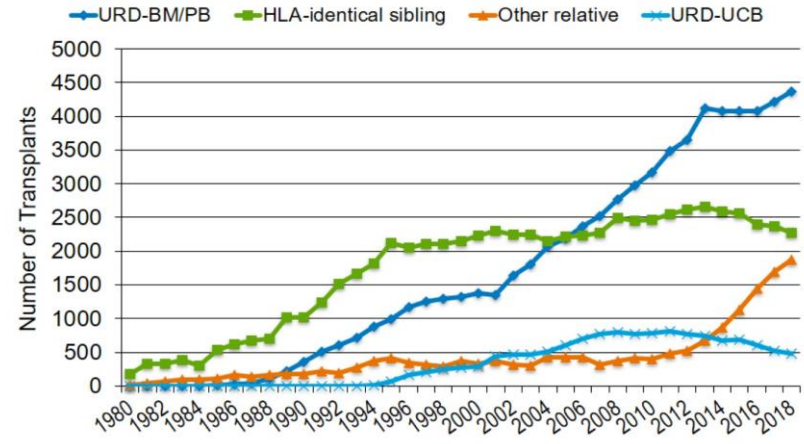
Allogeneic HCT Recipients in the US, by Donor Type



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Donor Types:

1) HLA matched sibling
2) Matched URD
3) Mismatched / haploidentical sibling
4) Umbilical cord blood

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Complications/Toxicity of HSCT

- Severely low blood counts (prolonged)
  - Infection
  - Risk of bleeding
  - Need for blood transfusions
- Infections
- GI side effects
- Mucositis
- Weakness, fatigue
- Graft versus host disease (allogeneic HSCT only), life threatening
- Need for re-immunizations
- Long-term follow-up needed

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Homework assignment

- Review patient resources available online including through Leukemia Lymphoma Society. Explore education materials and other offered resources to patients and their families.
  www.lls.org

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Questions?