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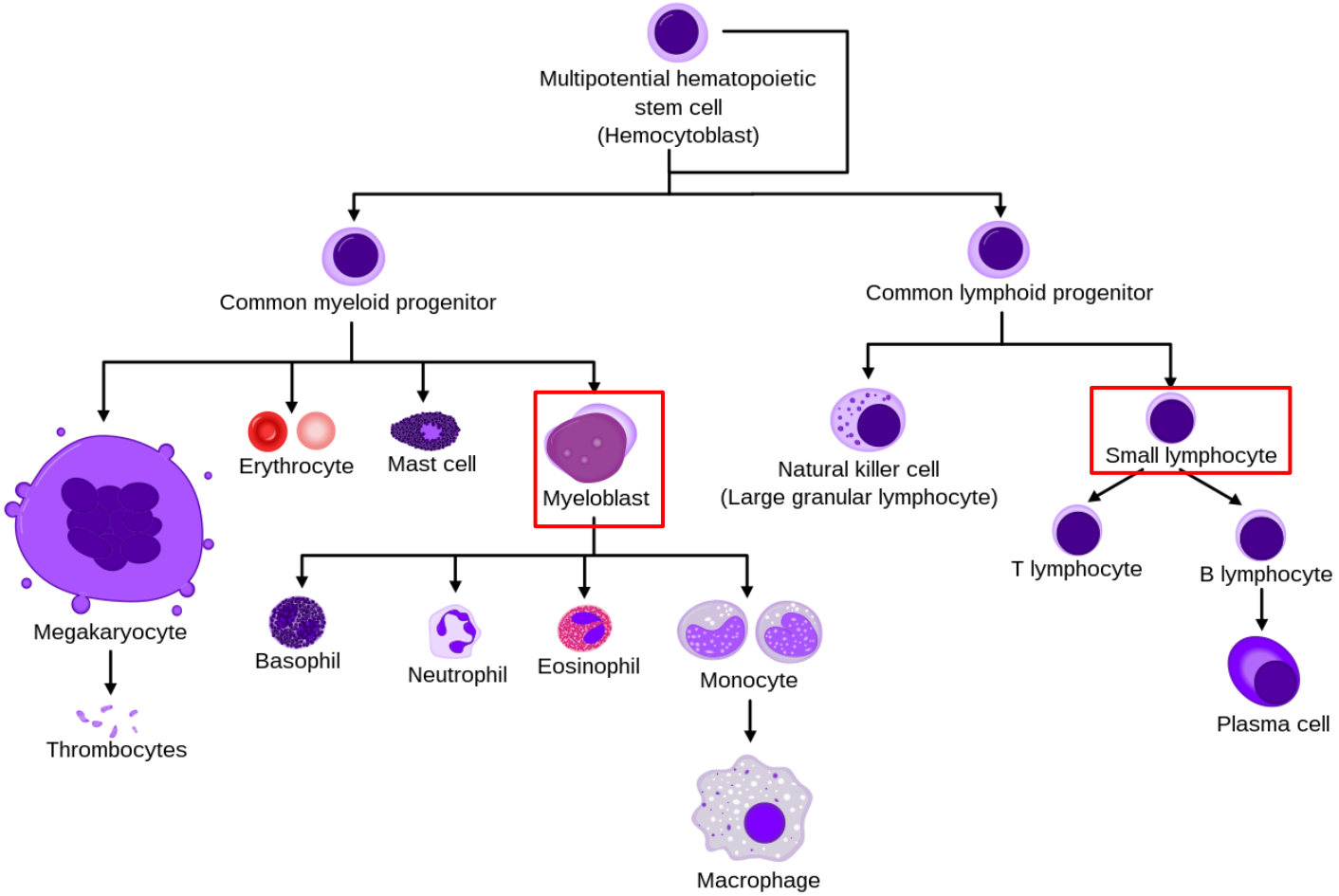
Pediatric Leukemia: Diagnosis and Treatment

CSHCS Annual Meeting 2023

Jessica Foley, MD

Basic science and pathophysiology of leukemia



- Myeloblast → Acute Myeloid Leukemia
- Lymphoblast→ Acute Lymphoid Leukemia

By A. Rad and Mikael Häggström, M.D. https://commons.wikimedia.org/w/index.php?curid=7351905

Epidemiology of pediatric leukemia

Spectrum Health Helen DeVos

How Common Is This Cancer?

Compared to other childhood cancers, childhood leukemia is fairly common.

	Common Types of Childhood Cancer	New Cases Per 100,000	Deaths Per 100,000
1.	**Leukemia**	**4.9**	**0.5**
2.	Brain and Other Nervous System Cancer	3.2	0.6
3.	Non-Hodgkin Lymphoma	1.3	0.1
4.	Hodgkin Lymphoma	1.2	0.0
5.	Thyroid Cancer	1.2	0.0
6.	Testicular Cancer	1.2	0.0
7.	Soft Tissue Cancer	1.1	0.2
8.	Bone and Joint Cancer	1.0	0.2
9.	Ovarian Cancer	0.7	0.0
10.	Kidney and Renal Pelvis Cancer	0.7	0.1

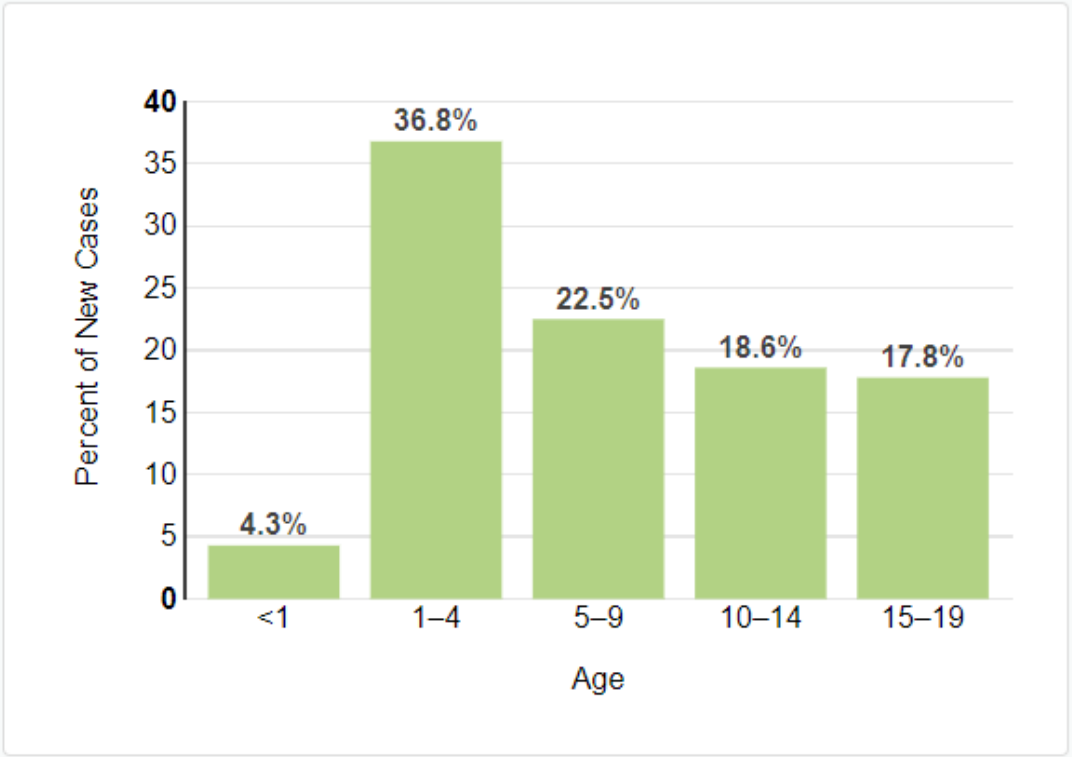
Childhood leukemia represents 24.9% of all new childhood cancer cases.

SEER 22 Incidence 2015–2019 & U.S. Mortality 2016–2020, Ages 0–19. Rates are Age-Adjusted

https://seer.cancer.gov/statfacts/html/childleuk.html

Epidemiology of pediatric leukemia

Percent of New Cases by Age Group: Childhood Leukemia



Childhood leukemia is most frequently diagnosed among children aged 1–4.

Median Age At Diagnosis
6

SEER 22 2015–2019, All Races, Both Sexes

https://seer.cancer.gov/statfacts/html/childleuk.html

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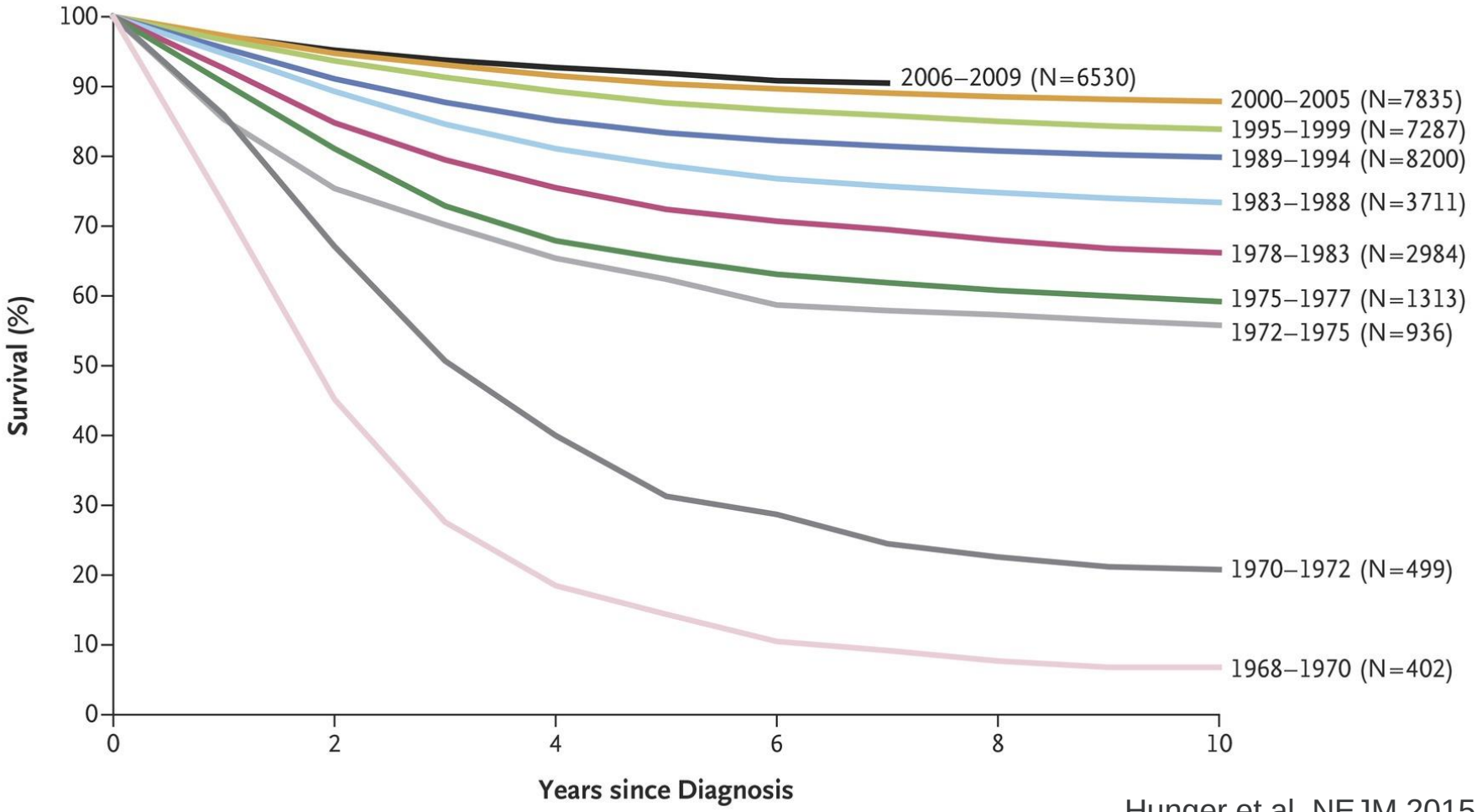
Overall survival in pediatric ALL COG trials 1968-2009



Hunger et al. NEJM 2015

Case study, patient SR

- 5 year old female presents to ED with right leg pain
  - Pain worsening over last few days, now with a limp
- Low grade fevers over the past several days
- Labs obtained in ED:
  - White blood cell count (WBC) 2,900
    - Absolute neutrophil count 660
    - No abnormal cells, ex lymphoblasts, present on blood smear
  - Hemoglobin 7.9 gm/dL
  - Platelets 71,000

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Clinical Presentation

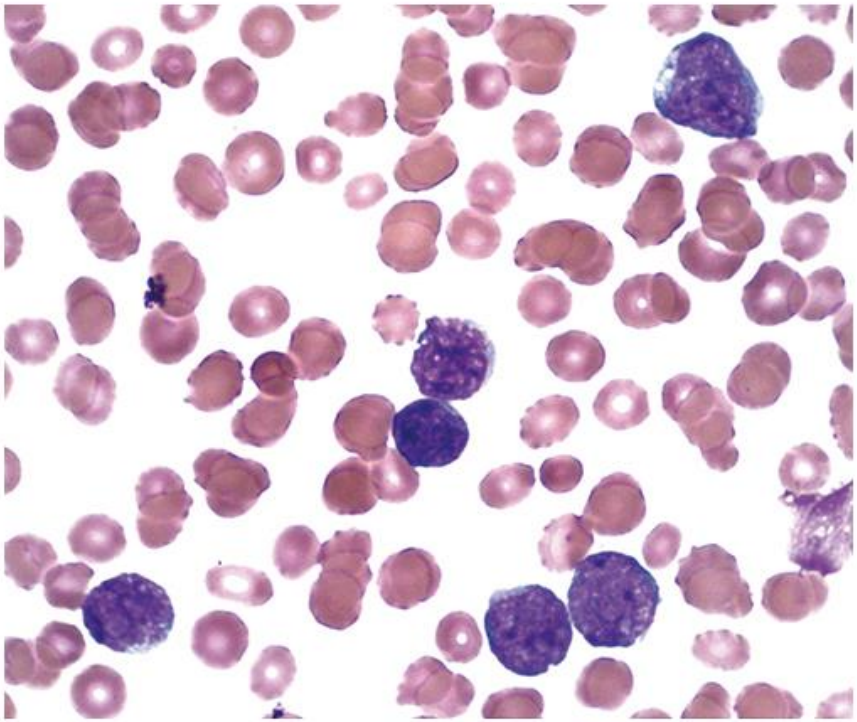
- Clinical symptoms as a result of leukemia infiltration in the bone marrow and subsequent pancytopenia
  - Marrow infiltration and expansion → Limp, bone pain
  - Anemia → Pallor, fatigue
  - Thrombocytopenia → Petechiae, bruising
  - Fever, infection
- Respiratory symptoms could indicate mediastinal mass
  - Dyspnea, cough, shortness of breath
- Headache could indicate leukemic infiltration of CNS
- Enlarged, often painless, testicle could indicate leukemic infiltration of testes
- Hepatosplenomegaly

Initial Diagnosis

- Pancytopenia present on CBC, not always with lymphoblasts present
- Lymphoblasts present on blood smear

White Blood Cell	1.37 !! (LP)
Red Blood Cell	2.39 ⌄
Hemoglobin	5.9 !! (LP)
Hematocrit	17.5 ⌄
Mean Cell Volume	73.2 ⌄
Mean Cell Hemoglobin	24.7 ⌄
Mean Cell Hemoglobin Concentration	33.7
Red Cell Diameter Width	15.6
Platelet	47 !! (LP)
Mean Platelet Volume	11.1 ⌃
Neutrophil Absolute Count	0.03 ⌄

Peripheral blood smear of acute lymphoblastic leukemia

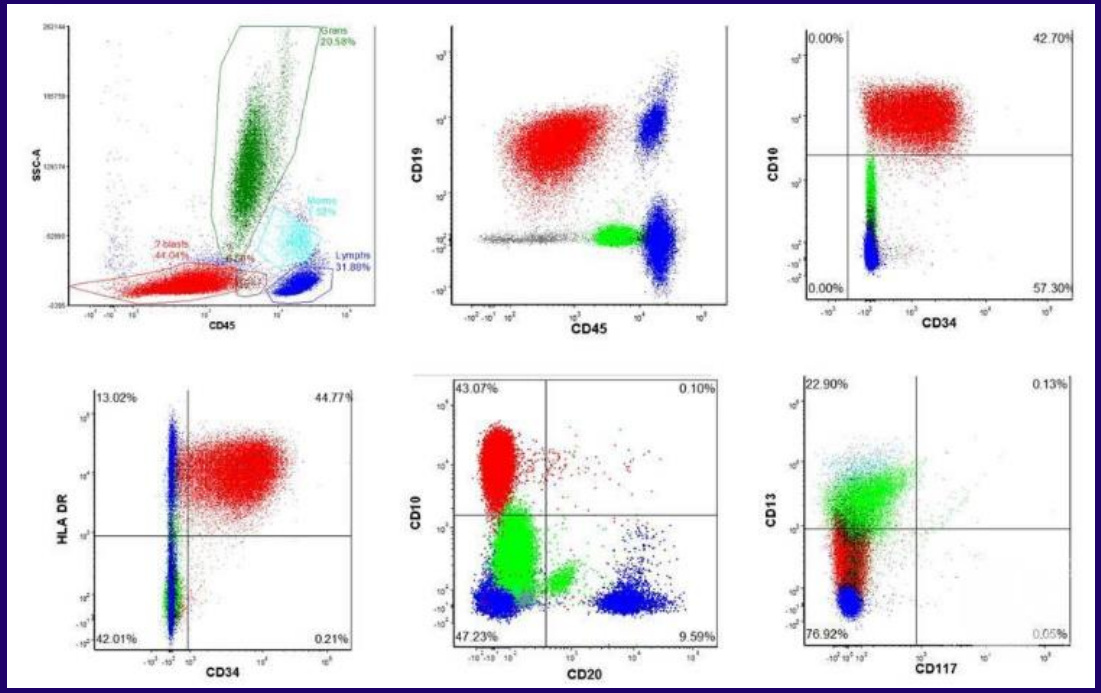


Flow Cytometry Diagnosis

- Cells flow past laser beam and measurements recorded
  - Thousands of cells per second
  - Can detect 1 cell out of 10,000

- determine make up of cell population by looking at surface protein expression = immunophenotype

- Red cells are lymphoblasts positive for CD 19, CD 10, characteristic of B cell ALL



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Staging

- Bone marrow biopsy and aspirate for flow cytometry and cytogenetics
- No stage 1, 2, 3, or 4
  - evaluate for extramedullary sites
- Lumbar puncture to evaluate for presence of leukemia
  - All patients receive chemotherapy into spinal fluid regardless of whether leukemia is present
  - Treatment includes increased frequency of spinal taps or even Cranial irradiation
- Physical exam of testicles to evaluate for presence of testicular disease

Testicular Involvement

- Present at diagnosis in 1-2% of males
- Associated with T-ALL, high presenting WBC
- Painless, hard, lumpy, enlarged testicle
- Involvement should be confirmed with biopsy
- Moving away from testicular irradiation if patient has a complete response obtained to Induction chemotherapy
- Isolated testicular relapse much less common with modern effective therapy

Case study, patient SR

- Bone marrow biopsy and aspirate shows lymphoblasts with flow cytometry confirming B cell Acute Lymphoblastic Leukemia
- Patient received port placement and started Standard risk Induction chemotherapy
  - Port placement facilitates easy of chemotherapy administration as well as blood draws
    - Risk of thrombosis and infection
- Leg pain resolved within 2-3 days, limp improved, no further fevers noted
- In total treatment will be 2.5-3.5 years of outpatient chemotherapy

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NCI Risk Groups in Childhood B-ALL

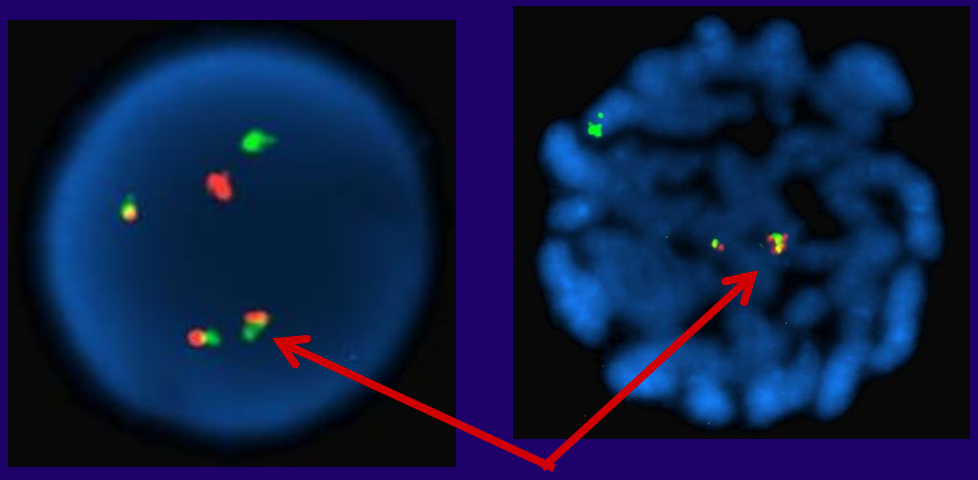
- Standard risk (~65% of patients)
  - Age 1-9.99 years
  - and WBC <50,000 at diagnosis
  - 5 year Event free survival (EFS) ~90%
- High risk (~35% of patients)
  - Age <1 year or >10 years
  - or WBC >50,000 at diagnosis
  - 5 year EFS 75-80% for non-infants
    - This is achieved with more intensive therapy
  - Outcome is still poor for infants with 5 year EFS ~40%
    - EFS is very poor if <3 months at diagnosis

ALL Risk Stratification continued

- Standard karyotype obtained
  - Able to assess for translocations, large deletions, as well as number of chromosomes (hypodiploid or hyperdiploid)
- Fluorescence in situ hybridization (FISH) to look for translocations, amplifications
- Cytogenetics are classified as favorable, neutral, or unfavorable
- Response to therapy, defined by presence/absence of minimal residual disease (MRD) after 1 month of chemotherapy, is the most important prognostic factor

Case study patient SR cytogenetics

- Enrolled on Children's Oncology Group protocol for standard risk leukemia
- On her 4th day of therapy the cytogenetics return and leukemia cells are positive for a translocation of chromosomes 12 and 21



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Sentinel Translocations in B-ALL

Cytogenetics	Incidence	Outcome	Comments
t(12;21)	20-25%	Excellent	Less common in patients >15 years
t(1;19)	5%	Now Neutral	Poor outcome in older studies. Higher incidence CNS disease
11q23 KMT2A-rearrangement	3%	Poor	75% of infants <1 year of age
t(9;22) BCR-ABL	4%	Poor with chemo alone	Incidence increases with age, improved outcomes with tyrosine kinase inhibitor
t(8;14), t(2;8), t(8;22)	rare	Treat like Burkitt lymphoma	

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How to approach new diagnosis ALL

1.) B or T cell? within hours

2.) CNS involvement? Testicular involvement? 24 hours

3.) National Cancer Institute (NCI) high risk or standard risk? diagnosis

4.) Cytogenetic findings 4 days

5.) Response to treatment

- End first month therapy (Induction) bone marrow 29 days

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Children's Oncology Group

- NCI supported consortium conducts phase 1, 2 and 3 clinical trials for children, adolescents, and young adults with cancer
- 200 children's hospitals in North American, Australia, New Zealand, and Europe
- 90% of the 16,000 children and adolescents diagnosed with cancer are treated at COG institutions
- ~100 active open trials at any time, including front line therapy for newly diagnosed disease
- Huge contributor to fantastic outcomes in B cell ALL

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COG Risk Adapted Approaches to Treatment

- Aimed at:
  - Identifying high risk subgroups and intensifying therapy to improve outcome
  - Identifying low risk subgroups de-intensifying therapy while maintaining excellent cure rates
- Continue to define what "high risk" and "low risk" mean
- As therapies improve prognostic factors may disappear
  - ex. t(1;19) used to be thought of as high risk but with more intense therapies these patients do just as good

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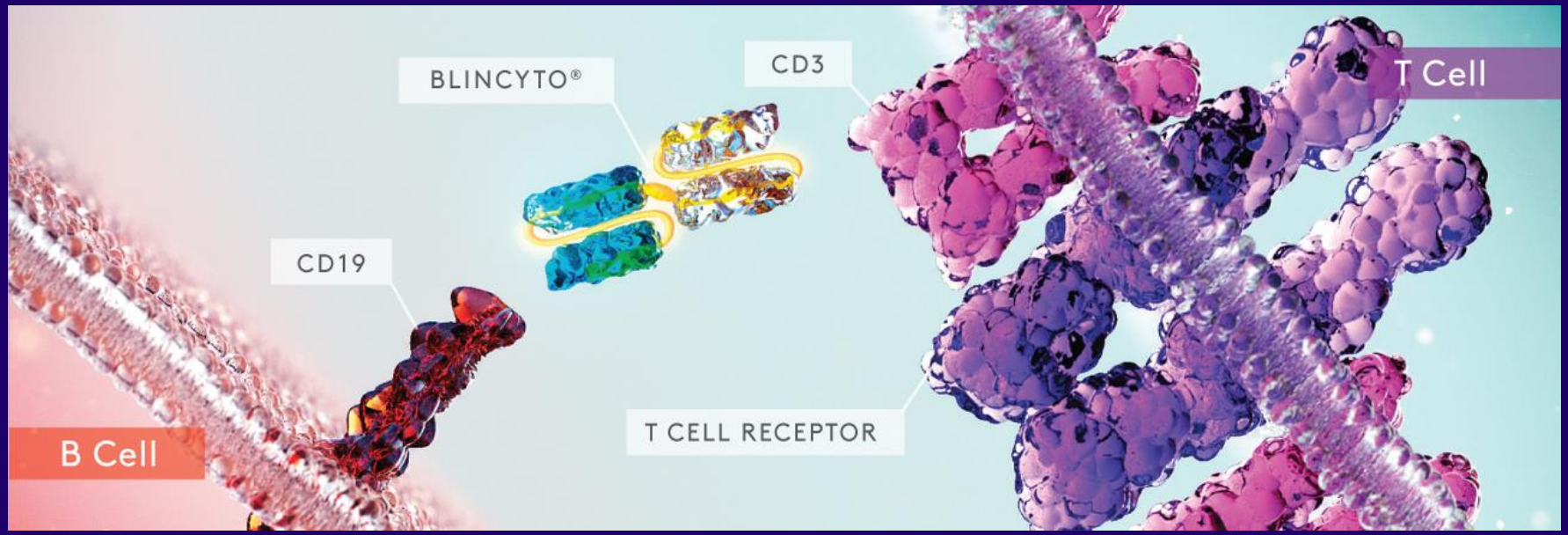
Current COG standard risk leukemia trial

- Randomized phase 3 trial (AALL1731) with blinatumomab for standard risk patients without favorable cytogenetics
- Bi-specific T cell engager (BiTE) antibody which bridges leukemia cell to T cell by targeting CD19 antigen on B cells



blincytohcp.com

Blinatumomab

- Showed promised in clearing minimal residual disease in refractory or recurrent patients
- Overall very well tolerated! However…..
- 28 day continuous infusion
  - Patients wear a backpack with chemo bag and pump inside
  - Port accessed throughout that time
- CD19 present on normal B cell as well so patients experience transient hypogammaglobulinemia and may need IV immune globulin infusions

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Case study, patient HR

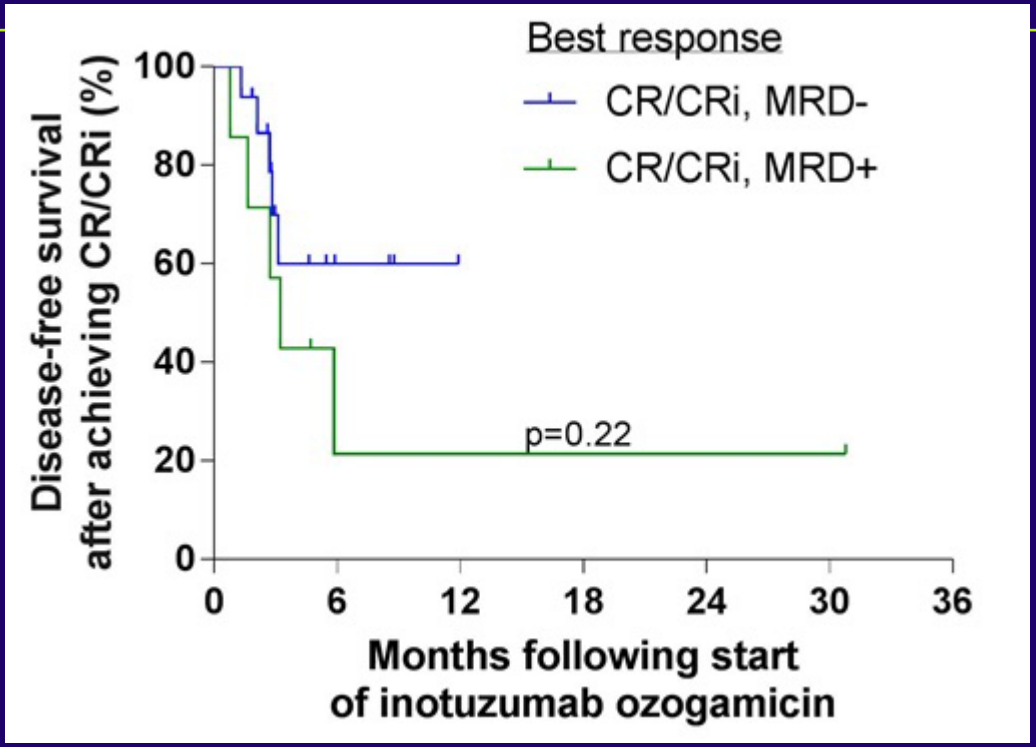
- 13 year old male comes to ED with history of fever x 4 days, malaise, decreased activity, decreased oral intake
- Sent from pediatrician office who felt hepatosplenomegaly on exam and was concerned with overall clinical appearance
- ED physician notes purulent drainage from nose
- Labs obtained:
  - CBC to look for pancytopenia
  - CMP, uric acid and phosphorus to look for electrolyte derangements given risk of tumor lysis syndrome
  - Blood culture
  - Type and screen

patient HR continued

- Patient decompensated and was admitted to PICU, progressed to septic shock and multi-organ dysfunction
  - Hypoxic respiratory failure, required intubation
  - Circulatory failure, required blood pressure support
  - Acute renal failure, required continuous dialysis
  - Found to have positive blood culture for pseudomonas
- Bone marrow biopsy and aspirate shows B cell Acute Lymphoblastic Leukemia
  - Initiated on chemotherapy for high risk B cell ALL
    - EFS 70-85% depending on cytogenetics and end of Induction minimal residual disease response

COG High Risk Leukemia Trial (AALL1732)

- Standard chemotherapy with randomization of the addition of Inotuzumab, monoclonal antibody targeting CD22
  - Linked to calicheamicin, a potent cytotoxic antitumor antibiotic

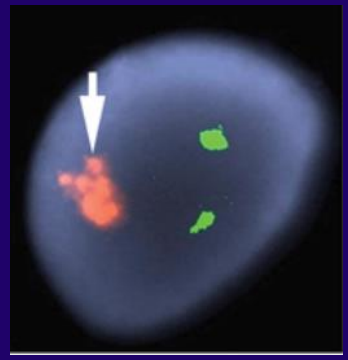


- Phase 2 COG study treated relapsed/refractory B cell ALL patients with Inotuzumab and found a response rate of 58%
  - In those responders 65% and no minimal residual disease

O'Brien et. al. Blood 2019

Case Study, patient iAMP

- 6 year old male presents with history of fatigue and pallor
- WBC 3,570, hemoglobin 4.2, platelets 86,000, WBC differential shows 22% blasts
- On day 4 of Induction fluorescent in situ hybridization (FISH) return with a positive intrachromosomal amplification of chromosome 21 (iAMP21)
  - iAMP21 is a high risk cytogenetic feature in B-ALL
  - patient initially treated like standard risk patient, but then additional chemotherapy added (high risk patient) when iAMP21 determined



Moorman A et. al. Blood 2007

Case study, patient iAMP

- End Induction (1st month) MRD by FISH 2.75%
- End Consolidation (2nd and 3rd month) MRD by FISH 1.25%
- Patient went into remission (no MRD) with intensified treatment with chemotherapy and received an allogeneic BMT from his sister
- He is 11 years out from transplant and doing well

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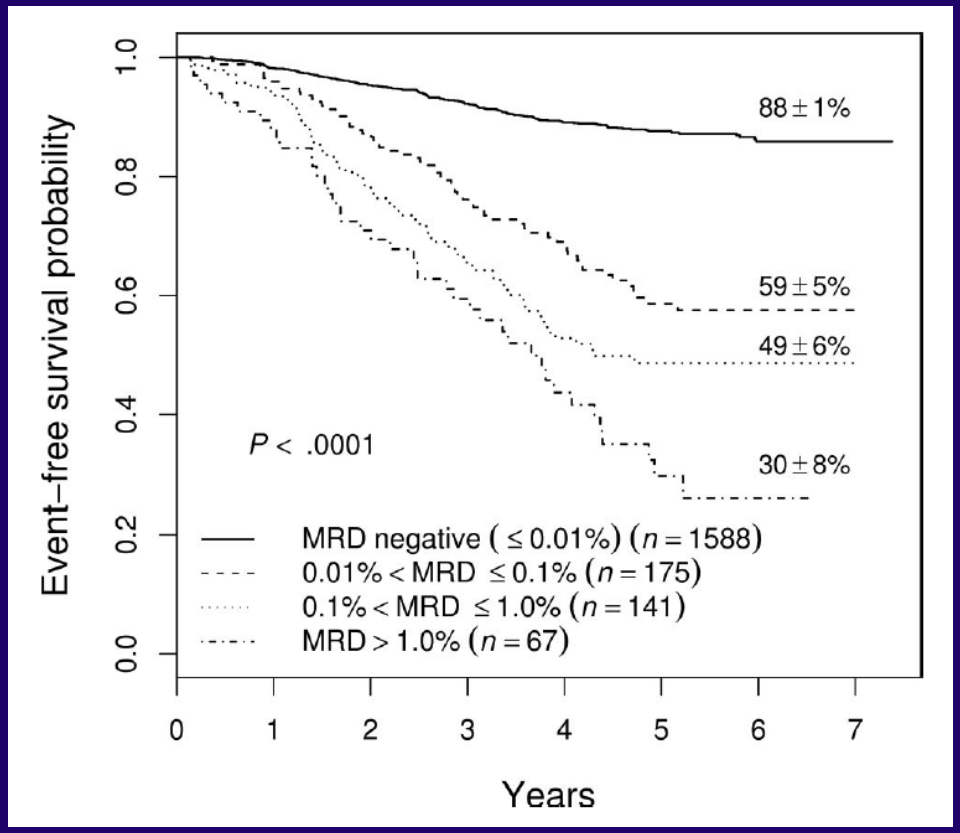
Factors that Influence Prognosis

- Baseline characteristics:
  - NCI risk group: Age, WBC, immunophenotype (B cell vs T cell)
  - Presence/ absence of extramedullary disease: CNS or testicular
  - Cytogenetics: strongly influences prognosis, treatment stratification, and sometimes the use of targeted therapies
    - Tyrosine kinase inhibitor (TKI) like Imatinib for t(9;22), Philadelphia chromosome positive ALL
- Response to therapy (evidence of minimal residual disease)
  - STRONGEST prognostic factor

Rapidity of Response

- Strongest prognostic factor!
- Historically we followed bone marrow evaluations (morphologic assessment) throughout Induction
  - M1 marrow would indicate remission (<5% blasts)
- Now relying on Minimal Residual Disease (MRD) measurements to define rapidity of response
  - Presence of cells following chemotherapy below level of morphologic detection
  - Techniques achieve a sensitivity of at least 1 cell in 10,000 cells (0.01%)
    - <0.01% MRD indicates remission

Importance of End Induction MRD in B cell ALL



<0.01% MRD

0.01% - 0.1% MRD

0.1% - 1% MRD

> 1% MRD

- 5-year event free survival (EFS) of B-cell ALL patients with varying degrees of end-Induction MRD

Borowitz M et. al. Blood 2015

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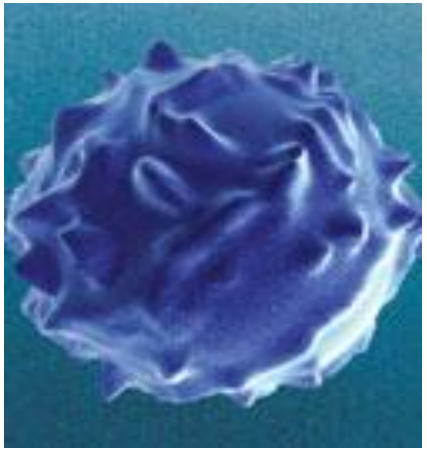
Bone marrow transplant indications

- Given poor outcomes with persistent minimal residual disease or relapsed disease bone marrow transplant indicated in *most* patients
- Patient receives high dose chemotherapy and usually total body irradiation
  - Normal hematopoietic cells destroyed or severely compromised
- Infusion of bone marrow stem cells from a matched donor (related, unrelated, or cord blood)
  - Reconstitutes hematopoietic stem cells in patient
  - Also serves as immune surveillance for any leukemia cells with graft vs leukemia effect (donor against cancer reaction)

Allogeneic (Non-Self) HSCT

- **Matched Sibling Donor**
  - Only 20-25% of children in need of an allogeneic transplantation have a matched sibling donor
- **Matched Unrelated Donor**
  - Worldwide 29.5 million registered donors
  - Chance of finding a donor ranges from 60-70% for Caucasians
  - Much lower chance for ethnic minorities
- **Unrelated Cord Blood**
  - Worldwide ~720,000 frozen cord blood units are available
  - No perfect match needed and immediately available
  - Limited by cell dose available (size of patient)
- **Haploidentical transplant (from one parent)**



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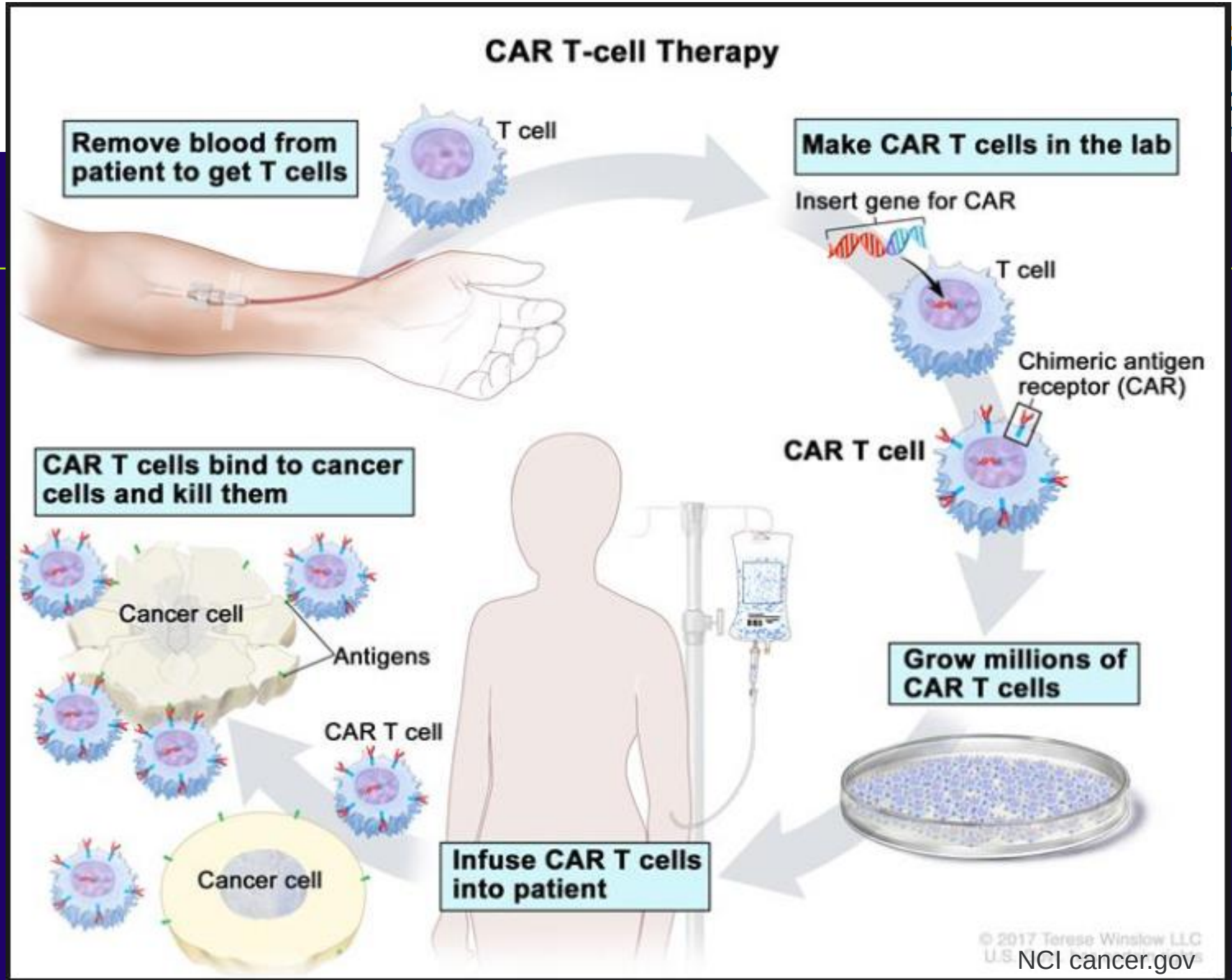
Toxicities of bone marrow transplant

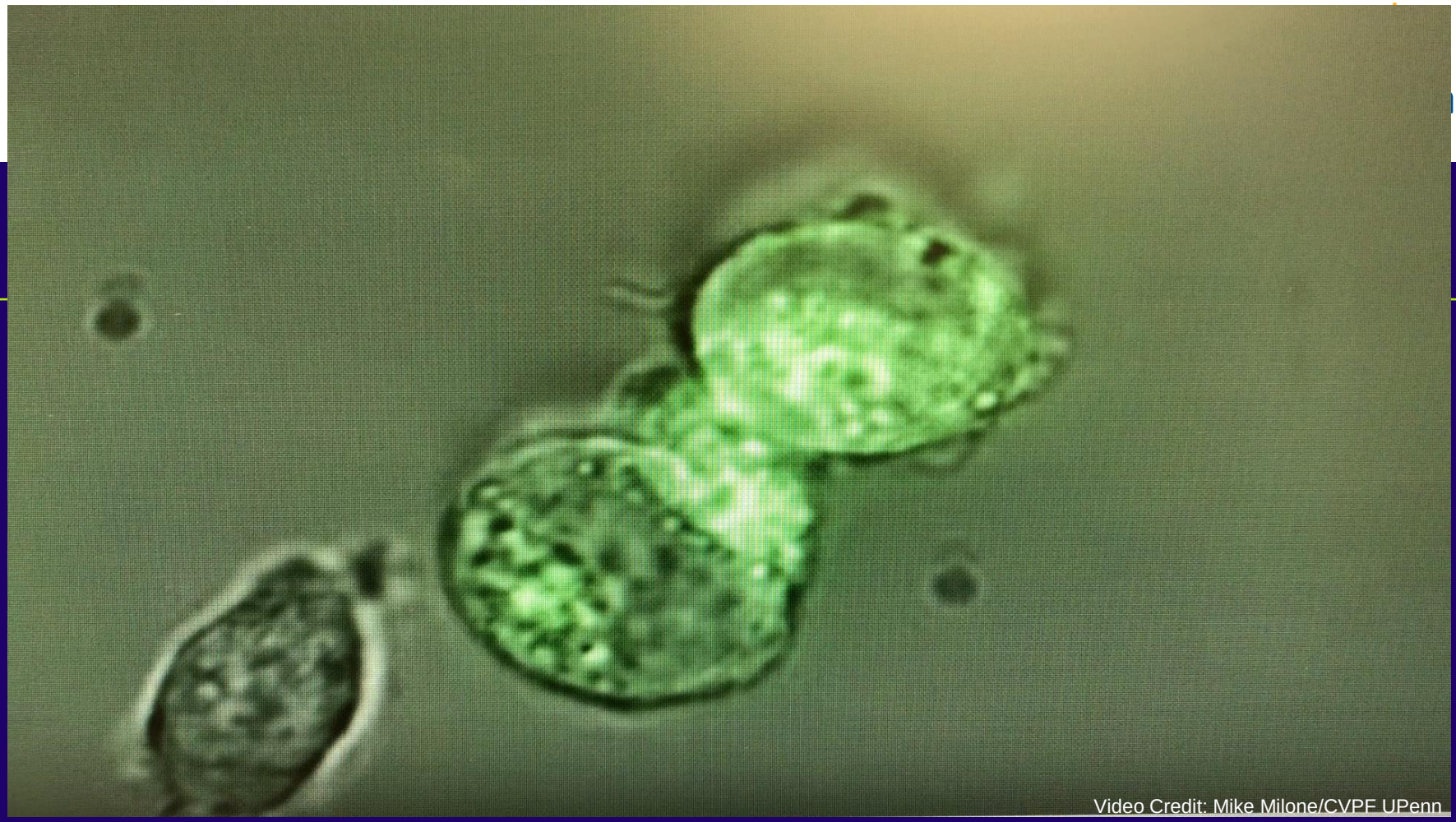
- Infection: viral, bacterial, fungus
- Graft vs host disease
  - Donor vs host disease- targets skin, liver, bowel
  - Both acute and chronic
- Secondary malignancy
- Delayed growth, puberty, hypothyroidism
- Cataracts, avascular necrosis, renal dysfunction
- Oral and dental problems

Chimeric antigen receptor (CAR) T cell therapy

- Collecting and using the patient's own immune cells to treat their cancer
- Current COG trial AALL1721 looking to do CAR T for B cell ALL patients with slow clearance of MRD



NCI cancer.gov

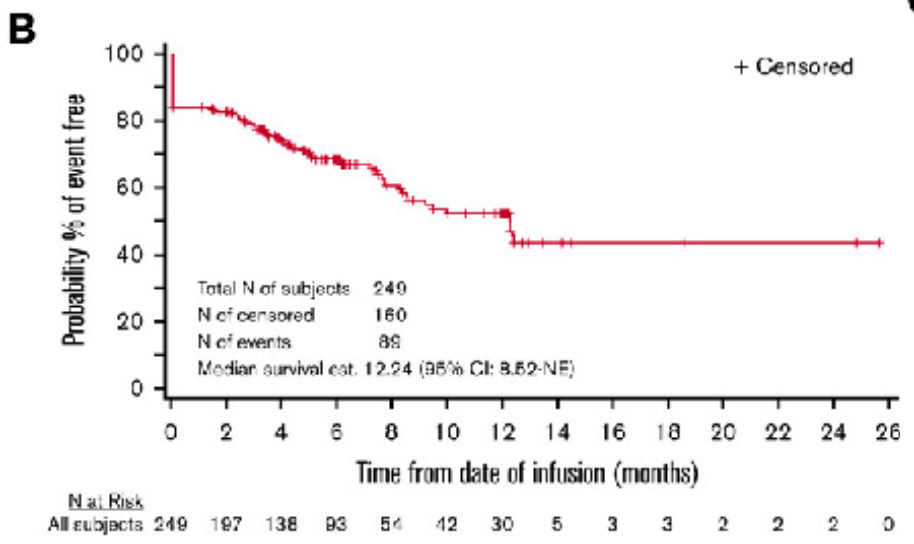


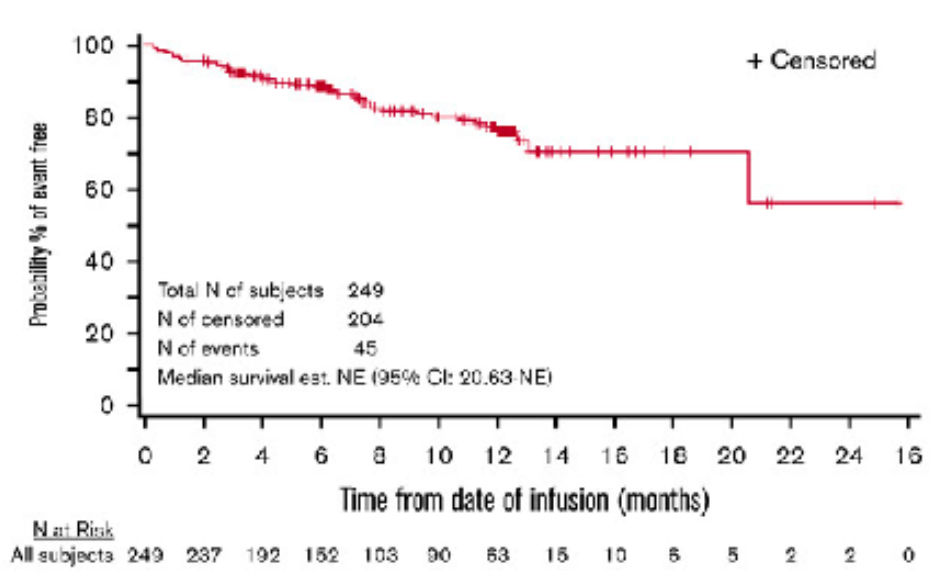
- Two lighter green cells are ALL blasts with one getting attacked by the smaller dark green CAR T-cell. Via the granzyme - perforin mechanism, holes are punched in the blast cell, and in turn leads to cell death

Real-World Tisagenlecleucel B-ALL Outcomes

1-yr EFS 52.4%

1-yr OS 77.2%



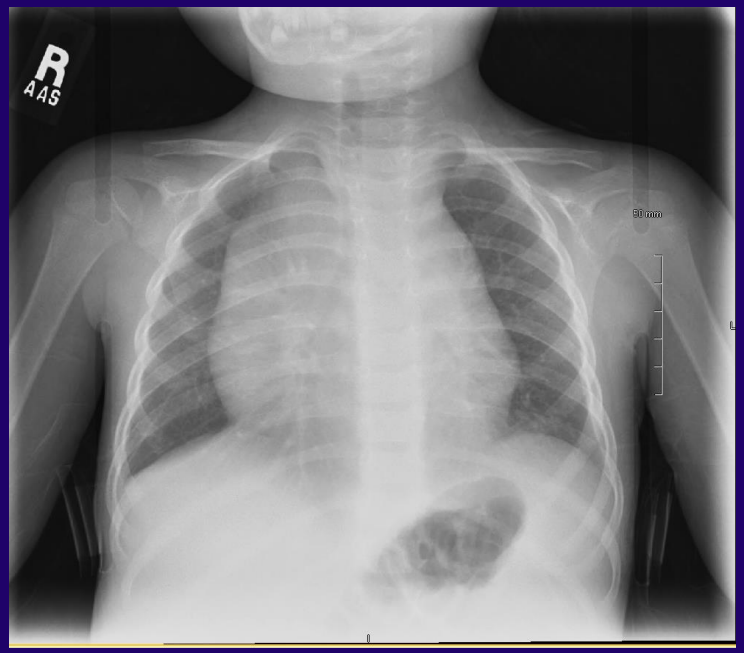


Relapsed / Refractory B-ALL Patients < 25 years (N=249)
Median follow-up: 13 months

Pasquini MC et al (CIBMTR). Blood Adv 2020

Case study, patient TC

- 3 year old female with febrile illness, found to have a WBC of 70,880 and 36% lymphoblasts on peripheral blood
- Flow cytometry shows positive CD2, CD7, CD5 consistent with T cell ALL
- CXR shows mediastinal mass
- Chemotherapy 2.5 years
- Several toxicities during Induction
  - thrombosis secondary to Peg-asp
  - hyperlipidemia secondary to Peg-asp and decadron



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T-cell acute lymphoblastic leukemia (ALL)

- ~15% of ALL are T-ALL
- Higher incidence CNS disease
  - cranial radiation used in treatment of CNS disease
- Often associated with a high WBC and mediastinal mass
  - Increased risk of tumor lysis syndrome
    - Elevations of potassium, uric acid, phosphorus
    - Can require dialysis
- *Historically* had worse outcome compared to B-ALL
  - EFS of 70-75%

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COG T cell study AALL0434

- Randomization with Nelarabine
- Found that Nelarabine improved outcomes in T cell ALL by decreasing CNS relapse risk
- Overall EFS 83%
- Nelarabine is now considered a standard of care by most for T cell ALL

Dunsmore et al., JCO 2020

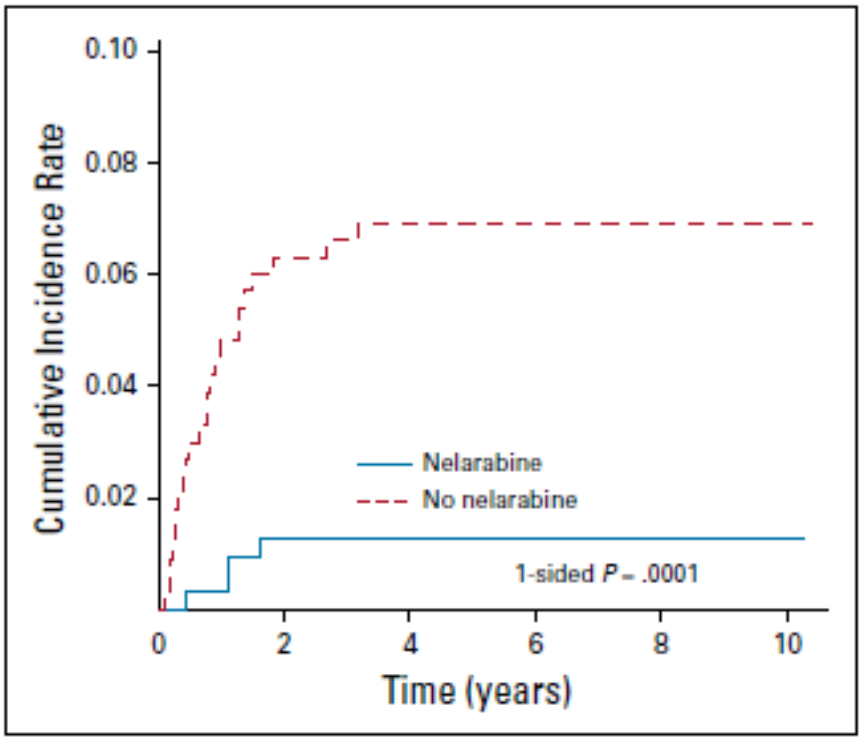
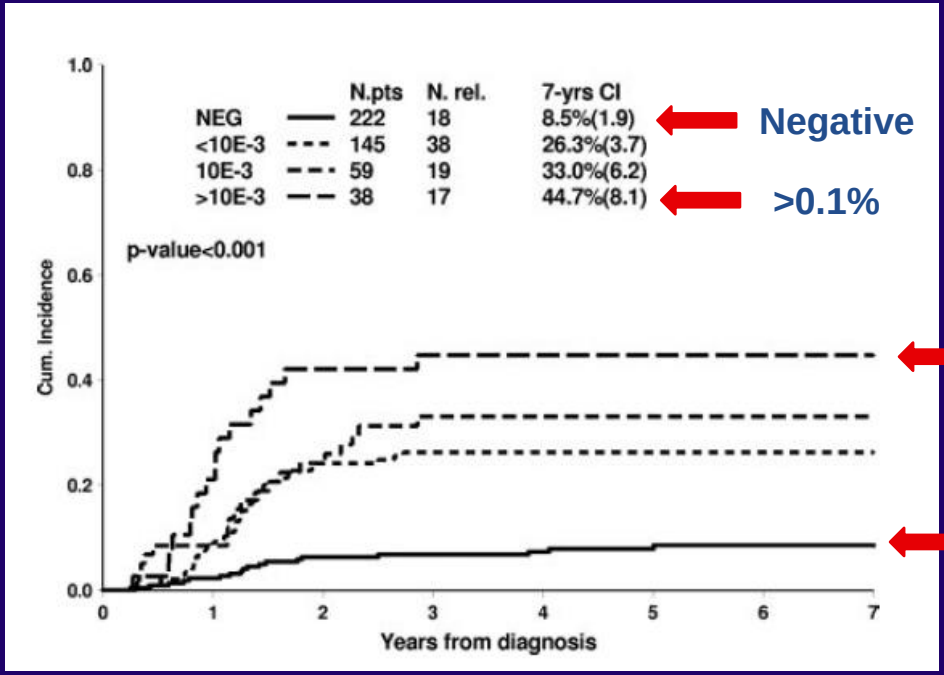


FIG 4. The 5-year cumulative incidence rates of CNS relapse (isolated and combined) in the nelarabine versus no nelarabine arms were 1.3% ± 0.63% and 6.9% ± 1.4%, respectively ($P = .0001$).

MRD in T cell disease

- MRD at the end of Consolidation (3rd month), *not Induction (1st month),* is most predictive of relapse
- Incidence of relapse in T cell patients according to various degrees of MRD end consolidation
- Incidence of relapse 44% if MRD >0.1% **end consolidation**



Schrappe et. al. Blood 2011

Case study, patient MLL

- 8 month old female 3 week history decreased energy and pallor
- WBC 626,000 with 80% blasts, hemoglobin 3.5 and platelets 19,000
  - Received emergency leukopheresis in the PICU
- Flow cytometry positive for CD19, CD34, negative for CD10
- Cytogenetics positive for the KMT2A gene rearrangement

Infant Leukemia

- Poor survival, especially with KMT2A gene rearrangement, which is present in 80% cases
- Infants without KMT2A do better with EFS 80%
- Patients >90 days KMT2A EFS 40%
- Higher incidence CNS disease
- Upcoming COG trial will give blinatumomab to KMT2A infants and also randomize to the addition of venetoclax
- Pilot study showed addition of 1 cycle blinatumomab to standard chemo showed early promising results of 90% event free survival at one year

Van der Sluis et al. *Blood* ***2021***

Case Study, patient AML

- 17 year old female with fatigue
- WBC 96,000 with 85% blasts
- Flow cytometry: CD33, CD 34, CD117, CD38 confirming a myeloid leukemia
- Cytogenetics positive for FLT3 Internal Tandem Duplication (FLT 3 ITD)

Pediatric AML

- OS estimated to be 60%, but large difference in survival depending on risk features (cytogenetics and MRD)
- Treatment for AML is risk stratified by cytogenetics and response to therapy:
  - Low risk:
    - Favorable cytogenetics or neutral cytogenetics with MRD negative
    - Disease free survival ~ 65%
    - 4-5 months intensive chemotherapy
  - High risk:
    - Unfavorable cytogenetics or neutral cytogenetics with MRD positive
    - Disease free survival much lower, some ~ 20%
    - 2-3 months intensive chemotherapy and then bone marrow transplant (BMT)

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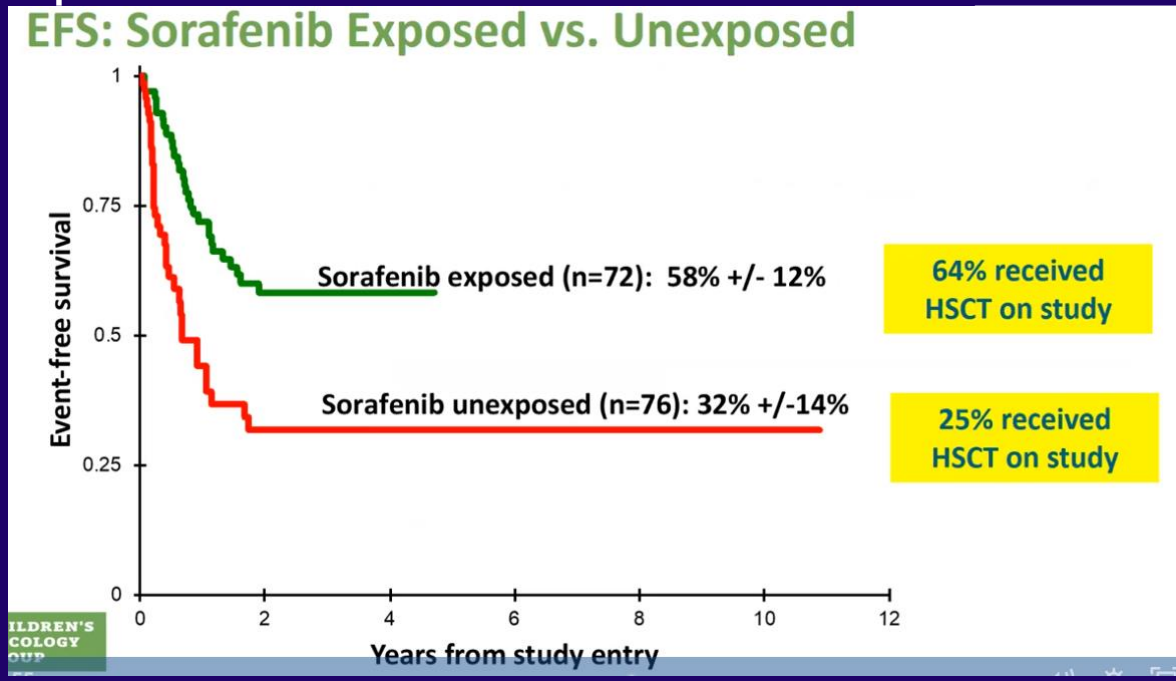
COG AML study, AAML1831

- FLT3 mutations particular poor prognosis in AML, overall survival of 20-30%
- Addition of a tyrosine kinase inhibitor (TKI) sorafenib improved EFS and more patients were able to receive BMT
- Currently COG trial uses TKI gilteritinib for FLT3 patients



Pollard et al. JCO 2022

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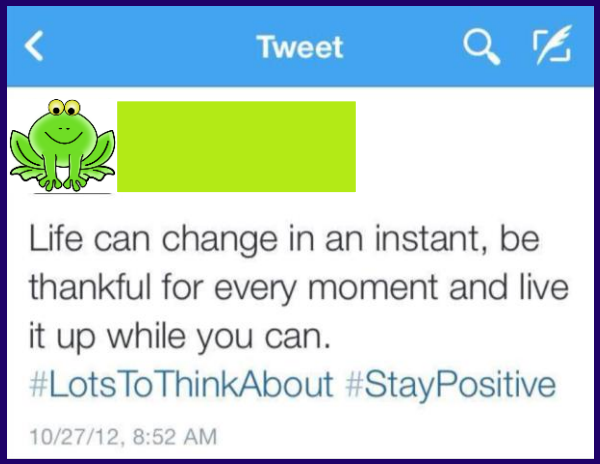
Patient AML

- Our patient enrolled on AAML1031 with sorafenib
- BM end Induction I = 0.5% MRD
  - end Induction II = 0.3%
  - end Intensification I = 0.3%
  - end Intensification II = 0.2%
    - one week later 4%



- Leukemia cells seemed to recover when WBC did
  - after additional cycle chemotherapy = 0.03%
  - patient then received double umbilical cord blood transplant as no matched donor
  - 30 days post double umbilical cord blood transplant 32% leukemia in Bone marrow
  - Patient died on hospice one month later

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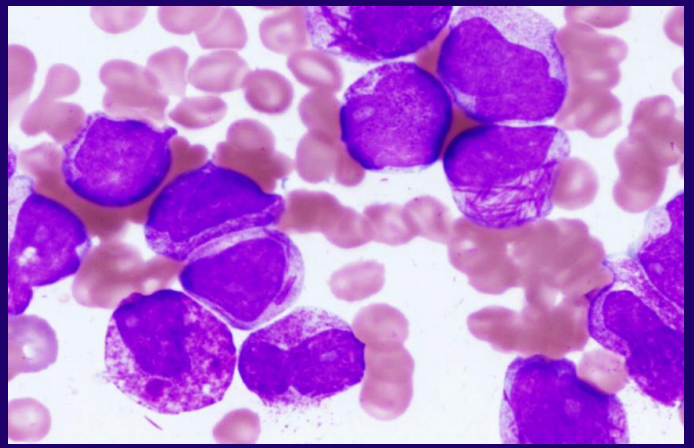
Case study, patient APL

- 17 year old female history of fever and abdominal pain
- WBC 32,000 with 87% blasts, platelets 19,000
- INR 1.8 (high), fibrinogen 158 (low), fibrin degradation products >20 (high)
  - concerning for disseminated intravascular coagulation (DIC)
- Peripheral blood shows blasts with Auer rods
- Cytogenetics positive for t(15;17) diagnostic of acute promyelocytic leukemia (APL)



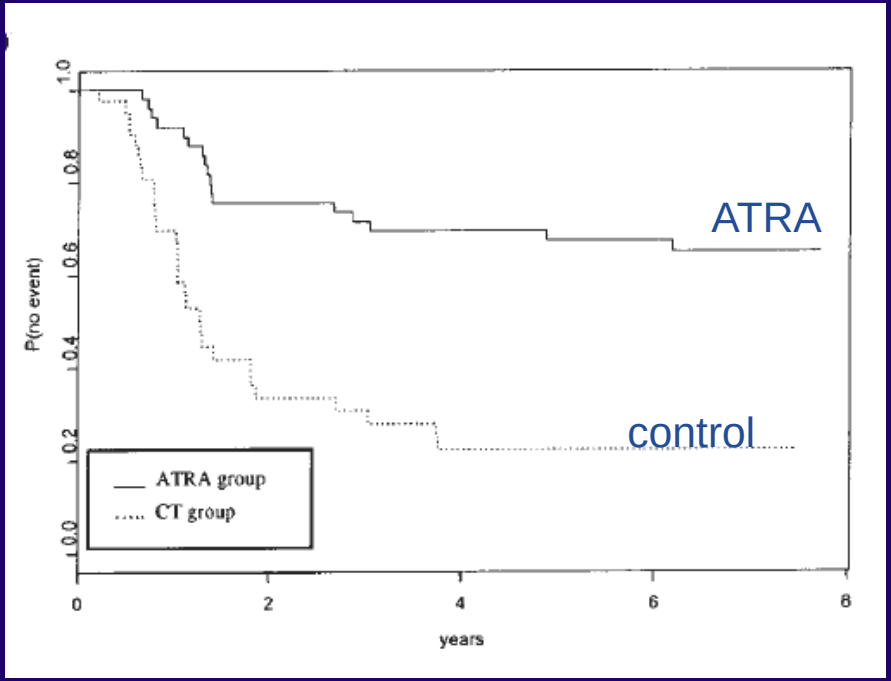
Tallman M, et. al. Blood 2009

Acute promyelocytic leukemia

- APL is a form of AML with a characteristic translocation of chromosomes 15 and 17
- t(15;17) joins PML-RARα which leads to the production of abnormal RARα protein which blocks myeloid differentiation at the promyelocyte stage of development
- Patients with APL often present with bleeding and DIC due to release of pro-coagulants from ruptured APL blasts
- Treatment with all-trans retinoic acid (ATRA) and arsenic trioxide is highly effective therapy for this specific form of AML

All trans retinoic acid (ATRA)

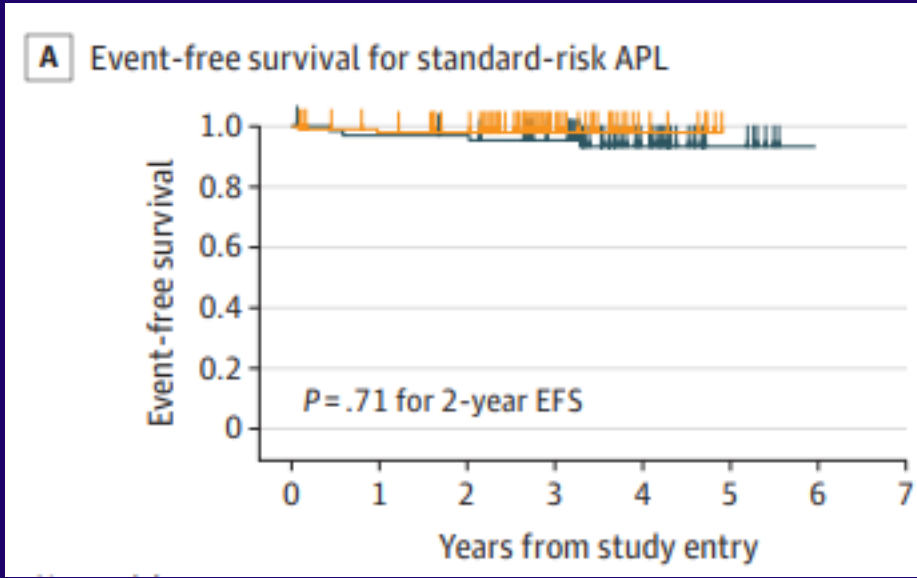
- ATRA was found to differentiate abnormal promyelocytes into mature granulocytes
- Initial randomized study comparing chemo alone to chemo + ATRA showed EFS of 63% with ATRA and only 17% in chemo alone

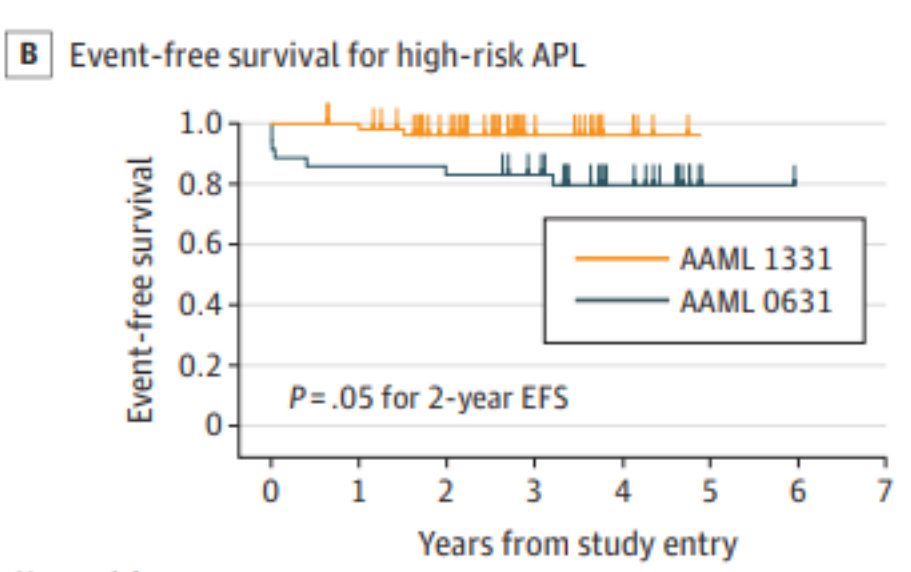


Fenaux P. et. al., Leukemia 2000

ATRA and arsenic in APL

- Arsenic trioxide showed promise in treatment of APL
- COG AAML1331 combined ATRA and arsenic and ***eliminated cytotoxic chemotherapy*** for almost all patients





- Results were outstanding!

Kutny. et. al., JAMA Onc 2022

Helen DeVos children's hospital
a member of SPECTRUM HEALTH

Thank you to:

Organizers for inviting me to speak and to

amazing team at Helen DeVos Children's Hospital for the outstanding care they provide our patients with leukemia