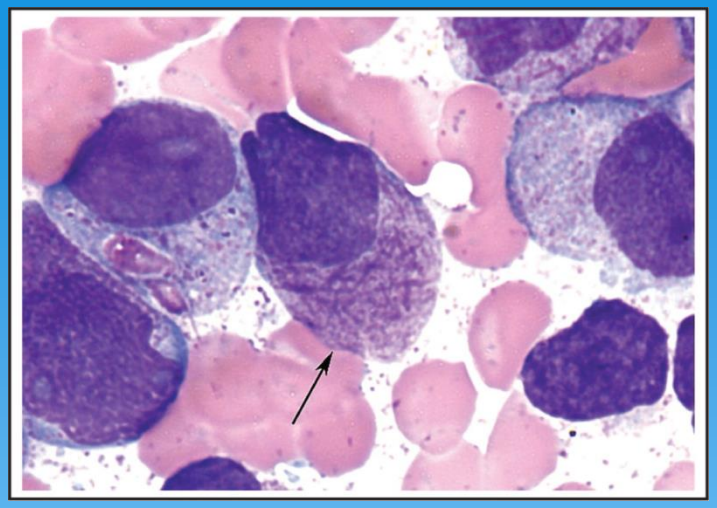


Acute Myeloid Leukemia

Angelina The

March 27, 2018

Outline

* Definition
* Epidemiology
* Diagnosis
* Treatment

AML History

* 1827, French physician Velpeau described a 63-year-old florist who developed an illness characterized by fever, weakness, urinary stones, and substantial enlargement of the liver and spleen. Blood of this patient had a consistency "like gruel."
* 1845, UK pathologist Bennett coined term "leucocythemia" to describe a series of patients who died with enlarged spleens and changes in the "colors and consistencies of their blood"
* 1856, German pathologist Rudolf Virchow coined term "leukemia." As a pioneer in the use of the light microscope, Virchow was the first to describe the abnormal excess of white blood cells.
* 1879, Bone marrow biopsy technique developed

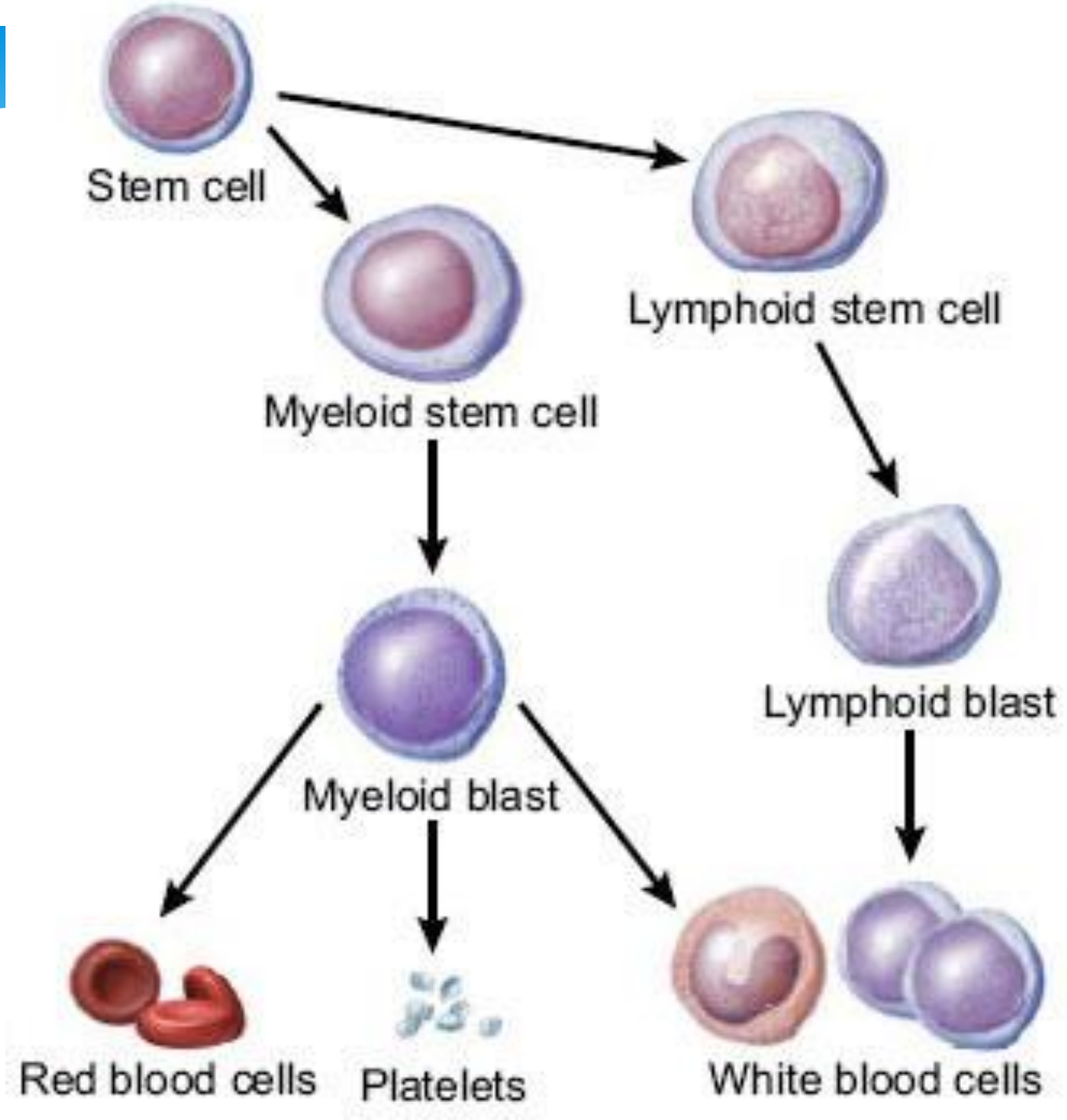
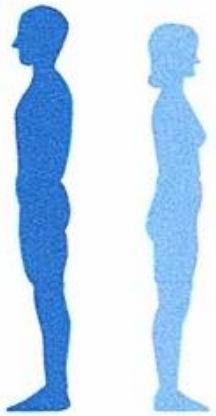

Stem cell
Myeloid stem cell
Lymphoid stem cell
Myeloid blast
Lymphoid blast
Red blood cells
Platelets
White blood cells

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2018 Estimates

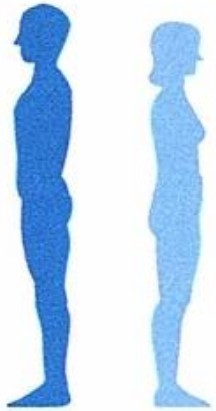
Estimated New Cases

Male			Female		
Prostate	164,690	19%	Breast	266,120	30%
Lung & bronchus	121,680	14%	*Lung & bronchus*	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%	Pancreas	26,240	3%
Leukemia	35,030	4%	Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%	Kidney & renal pelvis	22,660	3%
All sites	**856,370**	**100%**	**All sites**	**878,980**	**100%**



Estimated Deaths

Male			Female		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All sites	**323,630**	**100%**	**All sites**	**286,010**	**100%**



Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from the most recent observed data.

AML: Epidemiology

* Accounts for 90% of all acute leukemias in adults
* 20,800 new cases per year
* Median age of diagnosis – 67 years
* Overall survival in adults remains poor
  * <50% 5- year survival in those <45 years of age
  * <10% 5- year survival in those >60 years

AML: Causes and Risk Factors

* Underlying hematologic disorder
* Prior Therapy
  * Topoisomerases II
  * Alkylating agents
  * Radiation
* Environmental exposures
* Inherited conditions
  * Down syndrome, Diamond-Blackfan, dyskeratosis congenita, Fanconi anemia, etc
* Majority of cases are de novo

AML: Signs and Symptoms

* Neutropenia
  * Pustules, infections
* Anemia
  * Weakness, fatigue, DOE, palpitations
* Thrombocytopenia
  * Bruising/bleeding

AML: Evaluation

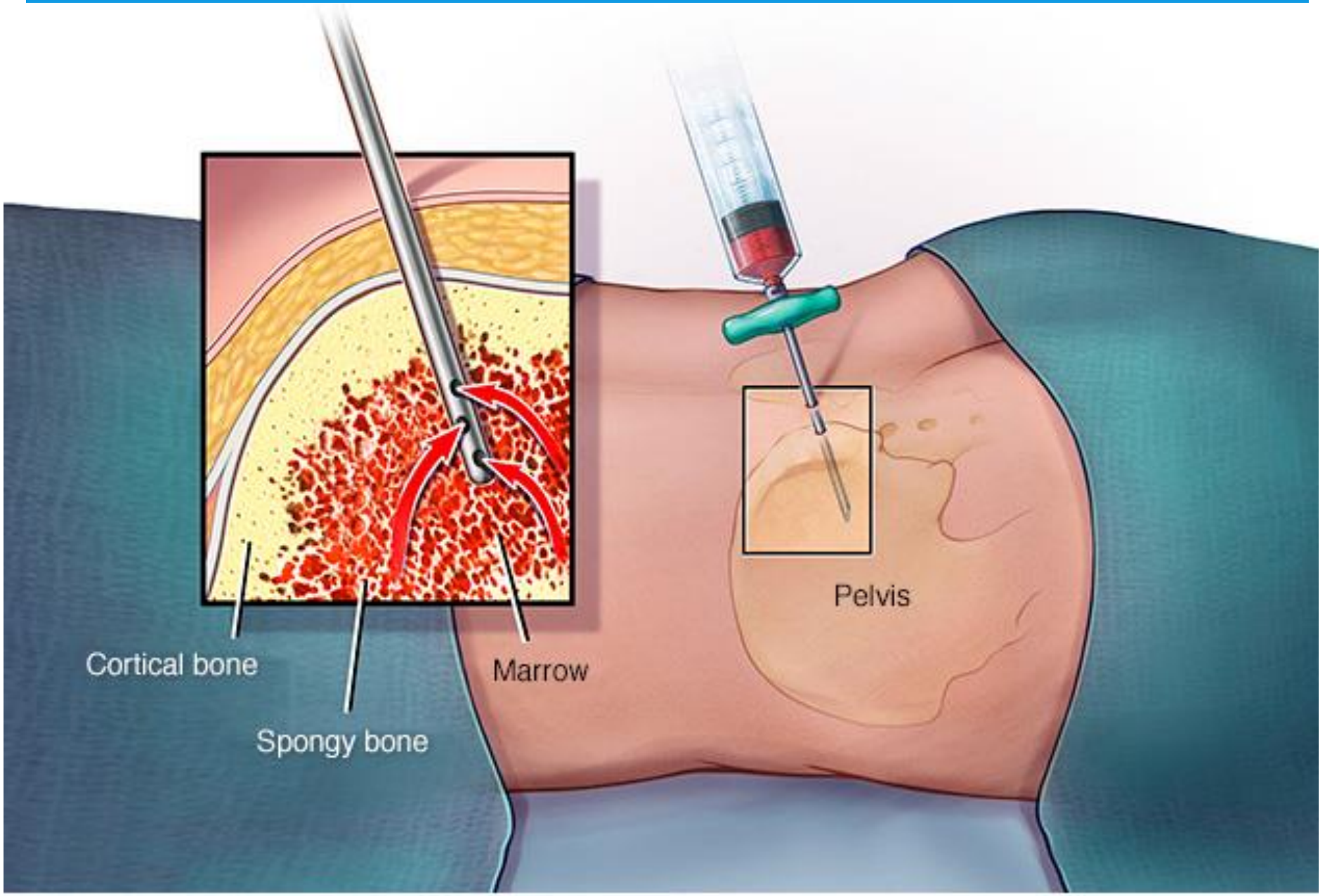
* Clinical data
  * Age, sex, ethnicity
  * History of hematologic disorders
  * Exposure to any cytotoxic therapy, radiation, immunotherapy, toxic substances
  * Confounding factors? Recent transfusions, growth factor tx, medications
  * Family history
  * Relevant physical exam and diagnostic studies

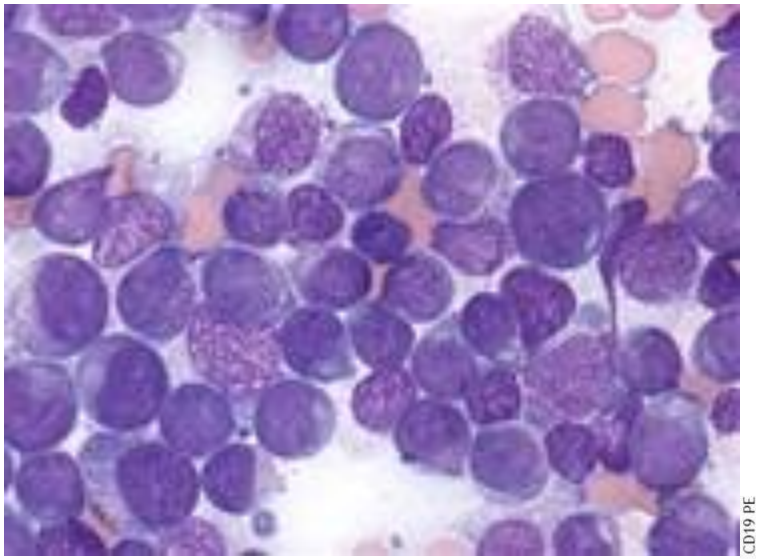
AML: Evaluation

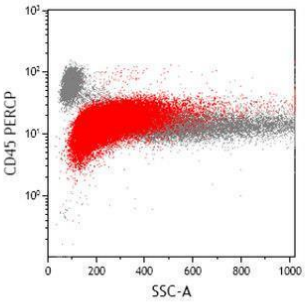
* Lab data
  * CBC with differential
  * LDH
  * PT/PTT
    * If abnormal: fibrinogen, D-dimer
  * Chemistries, uric acid, renal function, LFT's
  * Lumbar puncture if neuro symptoms present
  * HLA typing if HSCT under consideration
    * Available sibling donors

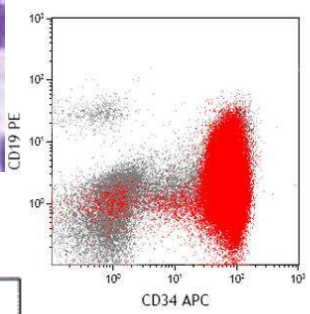
AML: Evaluation

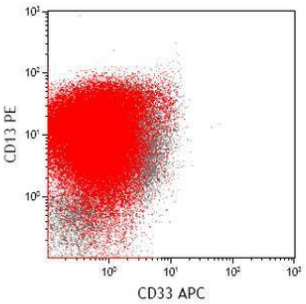
* Bone marrow aspirate and biopsy
  * Establish blast lineage (myeloid, lymphoid, ambiguous)
  * Perform risk assessment (favorable, intermediate, adverse)

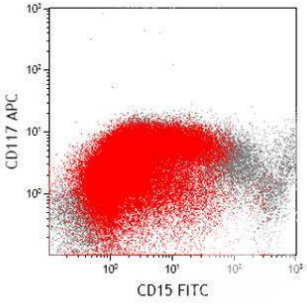












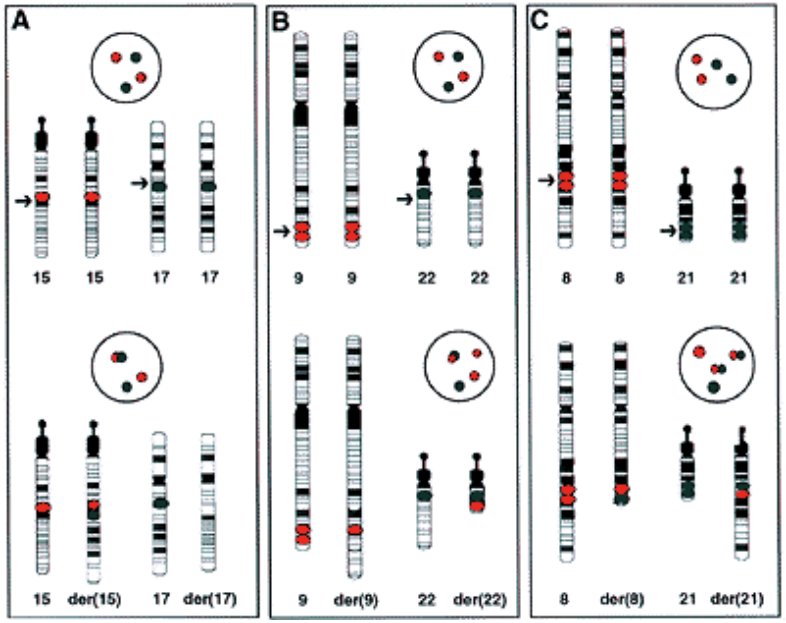
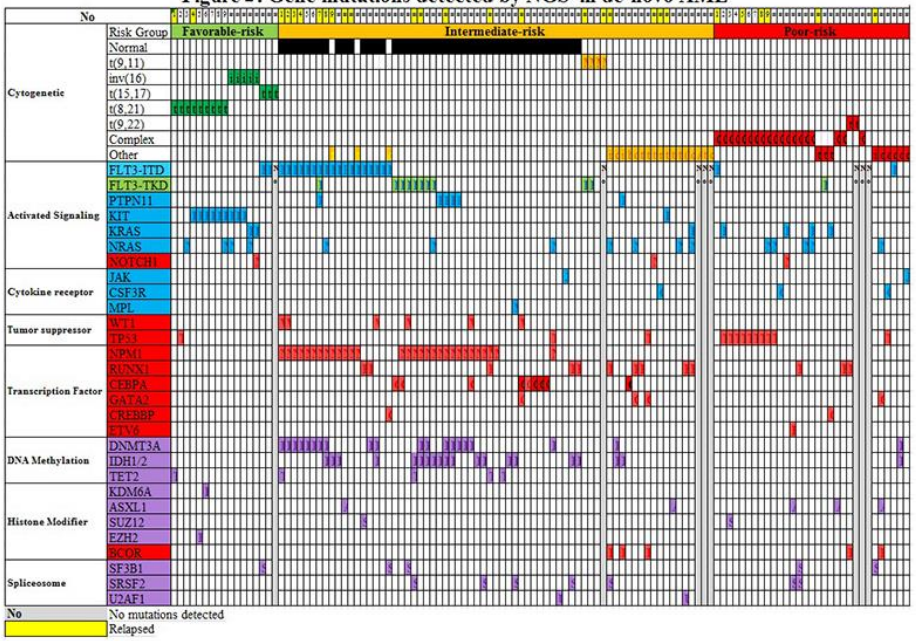


Figure 2. Gene mutations detected by NGS in de-novo AML



Diagnosis

* Established by the presence of 20% myeloid blasts in the bone marrow or peripheral blood

I've diagnosed AML. Now what????

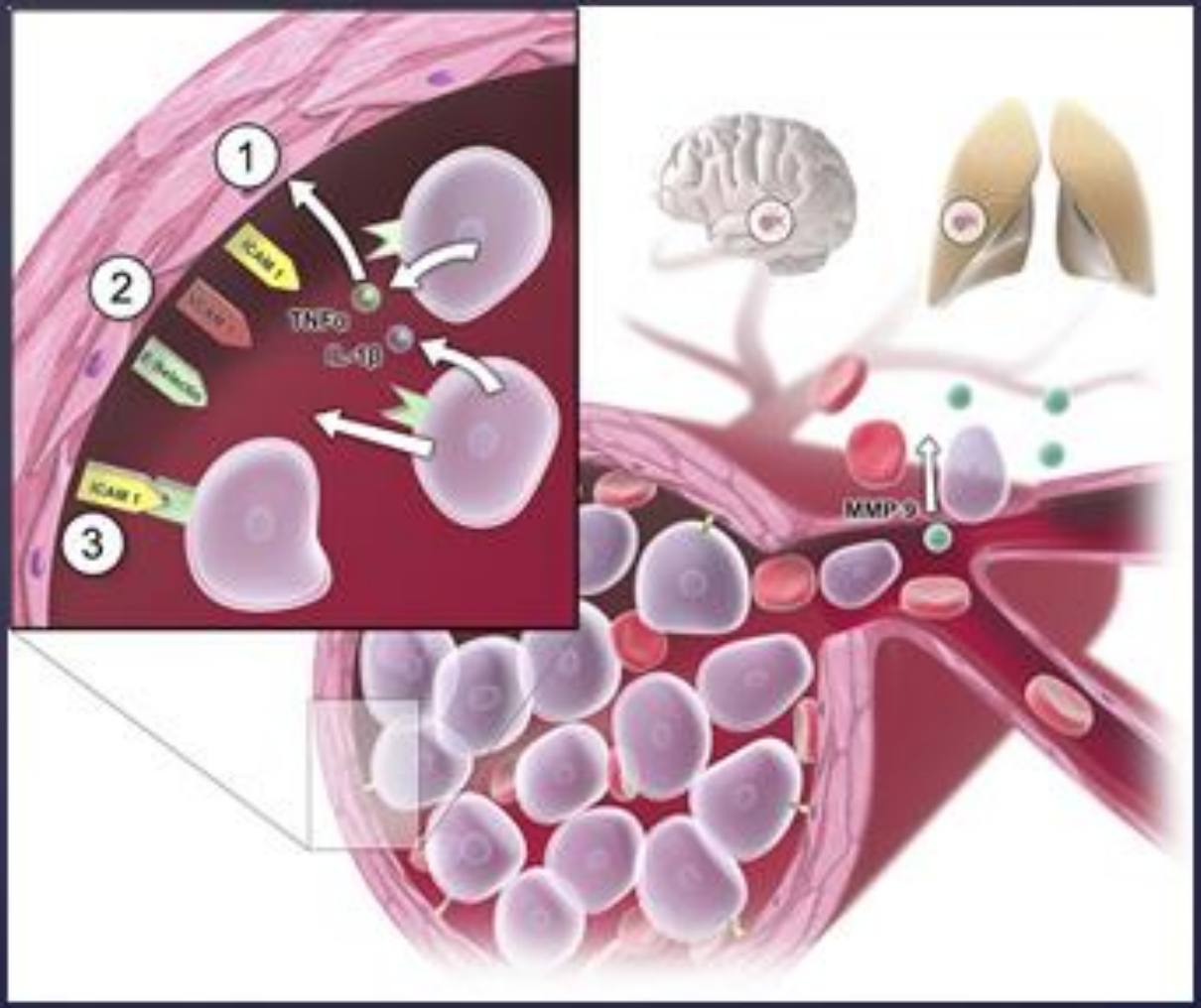
- Stabilize
  - DIC
  - Leukostasis/hyperviscosity
- Line placement
- ECHO
- IVF, alkalinized (D5W with 3 amps NaHCO)
- Allopurinol
- Rasburicase

- Discuss goals of care

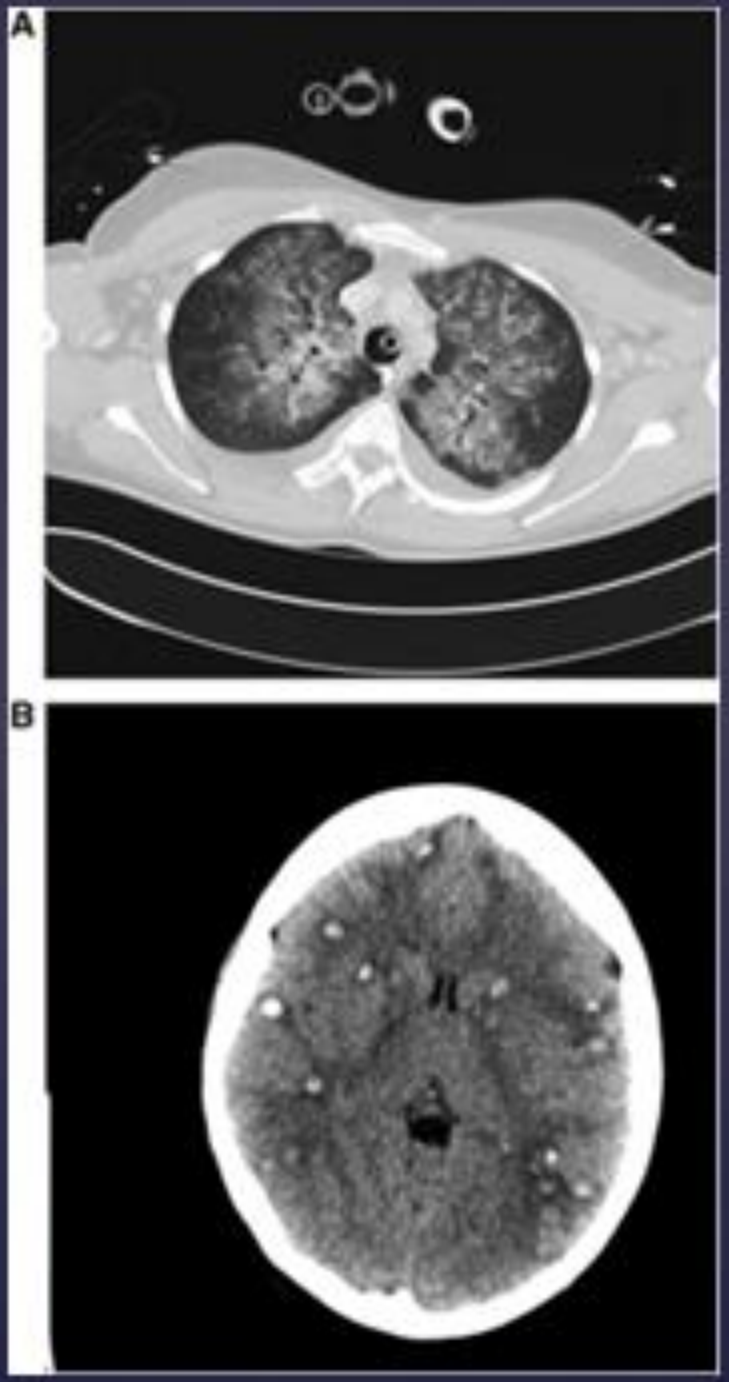
Hyperleukocytosis

* Occurs in ~5% of AML patients
* Blast count >100 x 10^9/L
* CNS, lungs and genitourinary systems most sensitive
  * Intracerebral hemorrhage
  * Altered mentation
  * Stupor
  * Priapism
* Early mortality increased in AML patients with HL

Pathogenetic mechanisms in leukostasis



Christoph Röllig, and Gerhard Ehninger Blood 2015;125:3248-3252


A
B

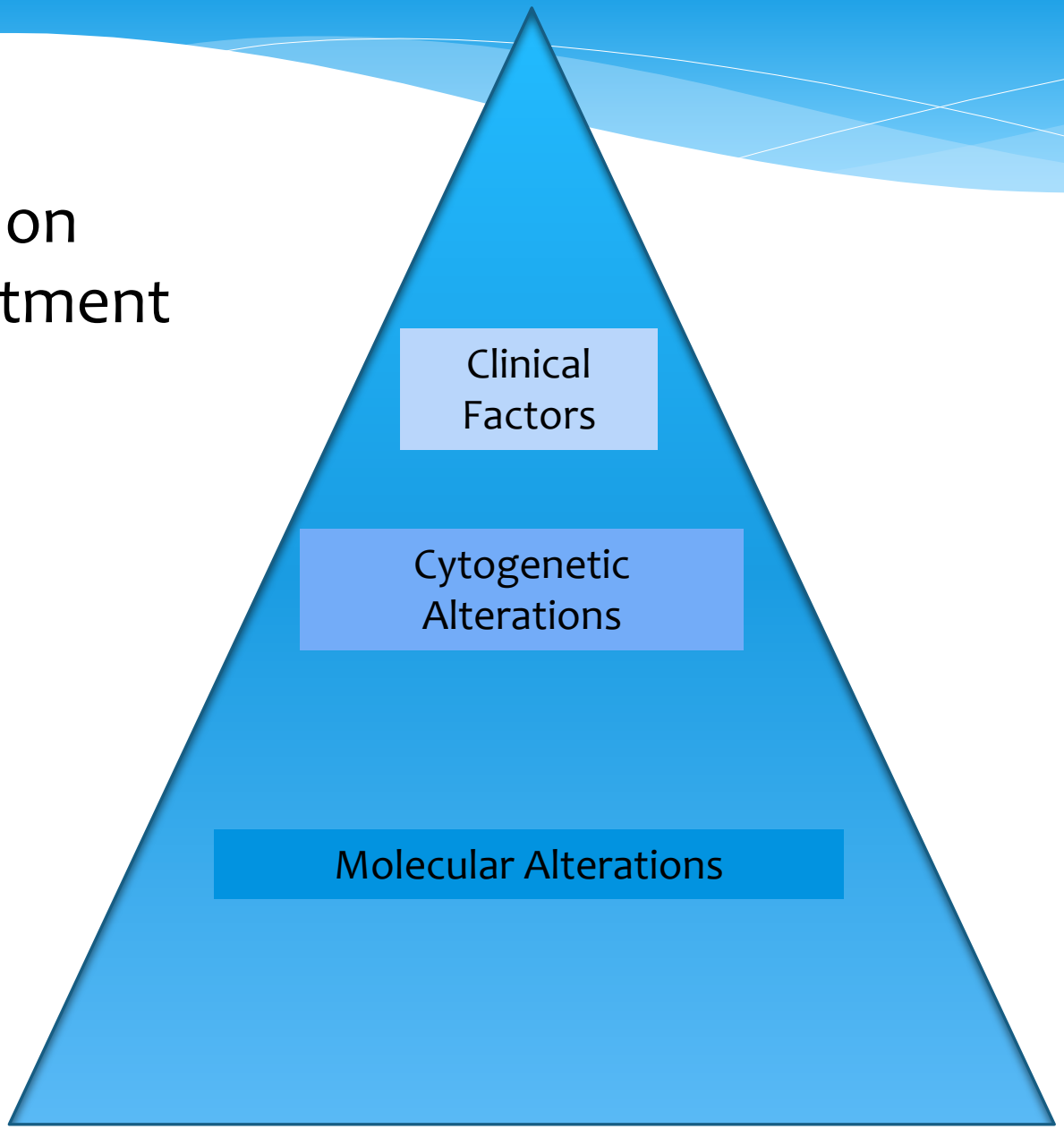
Leukoreduction Apheresis

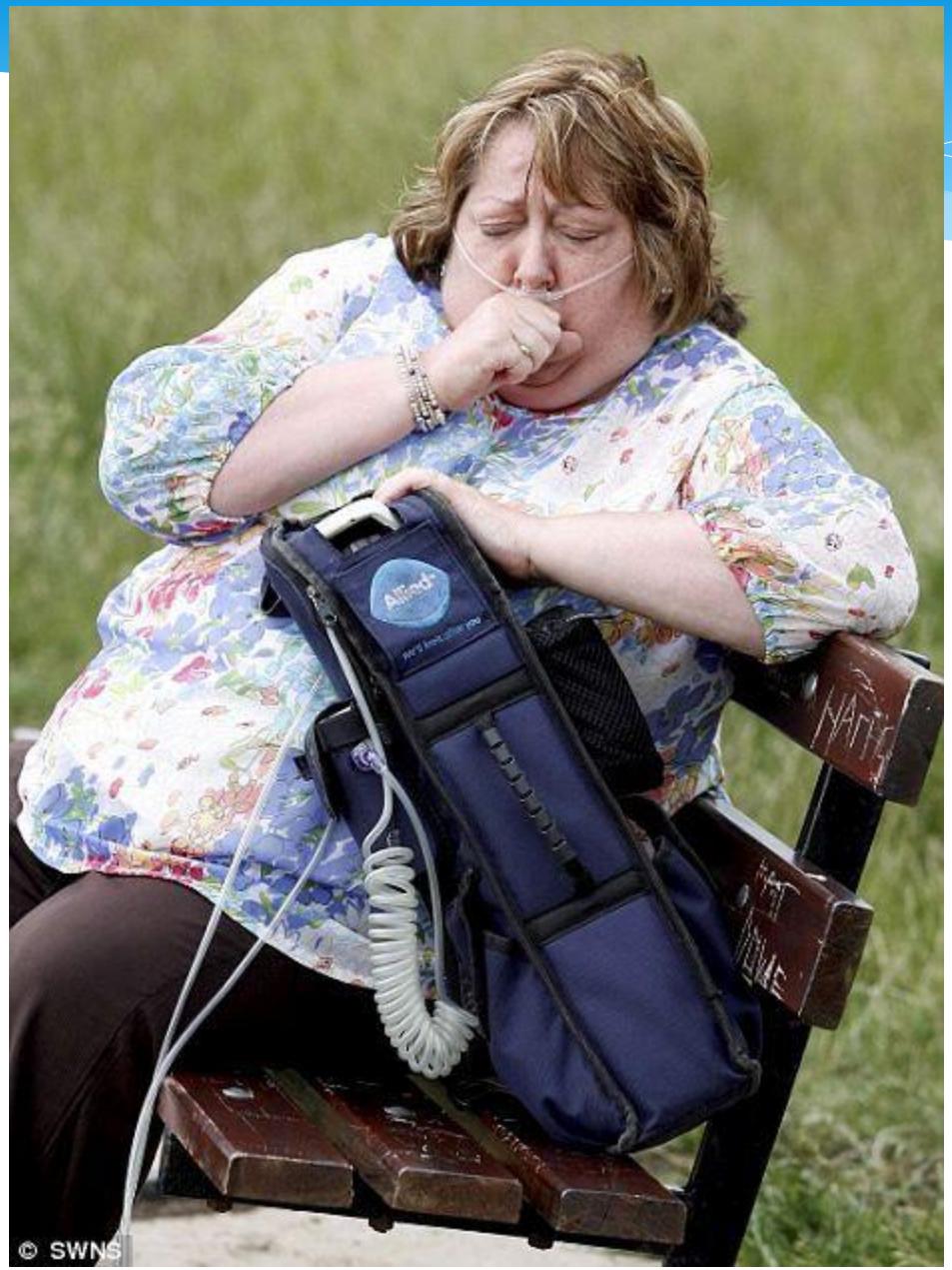
- Rapidly removes excess leukocytes by mechanical separation
- Single round of leukopheresis reduced WBC by 10-70%
- Debate:

  -Majority of leukemic burden in marrow

  -Beneficial clinical effect on early outcomes could not be shown consistently in clinical trials

Deciding on best treatment option…




Allied
© SWNS

Ed Whitlock, age 85

NY Times, 12/28/16

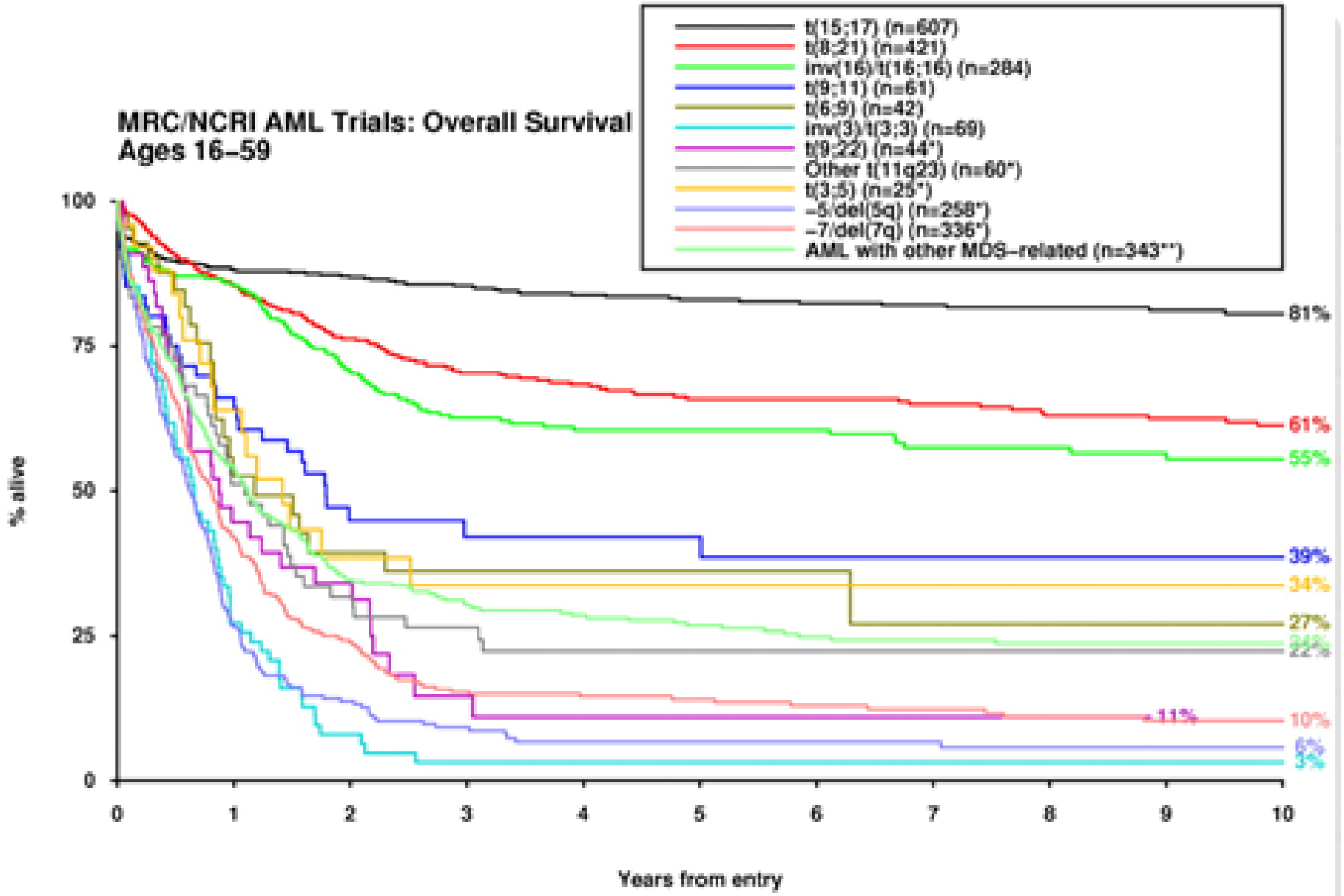
Adverse prognostic factors

* CNS involvement with leukemia
* Systemic infection
* Elevated white blood cell count (>100,000/mm3)
* Treatment-induced AML
* History of MDS or another antecedent hematological disorder.

Table 2. Current Stratification of Molecular Genetic and Cytogenetic Alterations, According to ELN Recommendations.*

Risk Profile	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD (normal karyotype) Biallelic mutated *CEBPA* (normal karyotype)
Intermediate-I†	Mutated *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse‡
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *GATA2–MECOM (EVI1)* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *KMT2A* rearranged –5 or del(5q); –7; abnl(17p); complex karyotype§

N Engl J Med 2015; 373:1136-1152



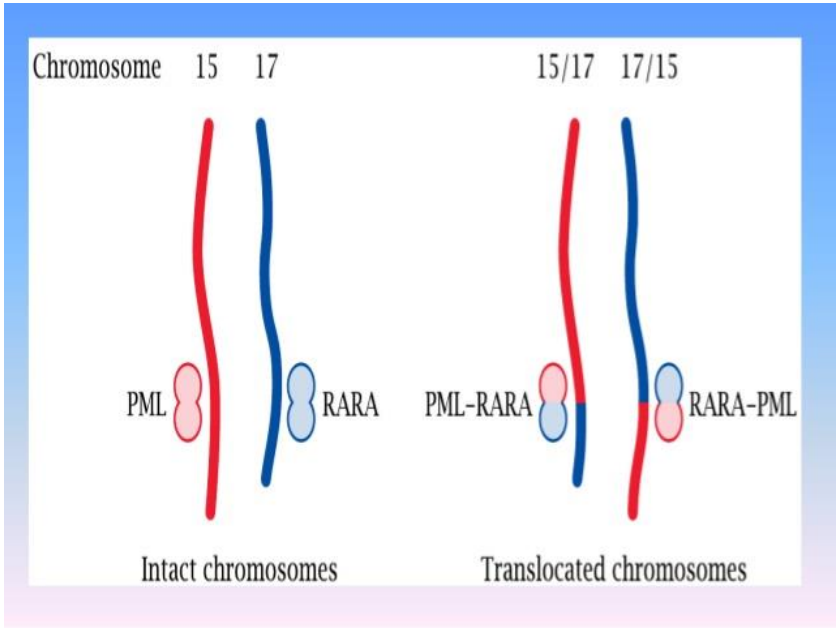
Impact on karyotype entity on survival

Cytogenetically Normal AML

* Favorable
  * No FLT3 mutation
  * Mutated CEBPA
  * Mutated NPM1
  * IDH1/IDH2
* Unfavorable
  * FLT3-ITD mutation
  * TP53 mutation
  * DNMT3A
  * KMT2A

Acute Promyelocytic Leukemia

* Translocation typically between chromosome 17 and 15% (variant translocations between 5, 11, 17 have been described)



Acute Promyelocytic Leukemia

* Accounts for ~10% of AML
* Occurs at any age
* DIC/hemorrage
* Unique therapeutic considerations
  * ATRA
  * Arsenic trioxide

AML: Treatment Approach

* Disease factors
  * Biology of AML
* Host factors
  * Comorbidities
  * Physical status and cognitive function
  * Polypharmacy
* Patient wishes
  * Dependency, quality-of-life, caregiver burden of disease

Treatment with Curative Intent

Induction

Day#14
BMBx

Complete Remission

Consolidation

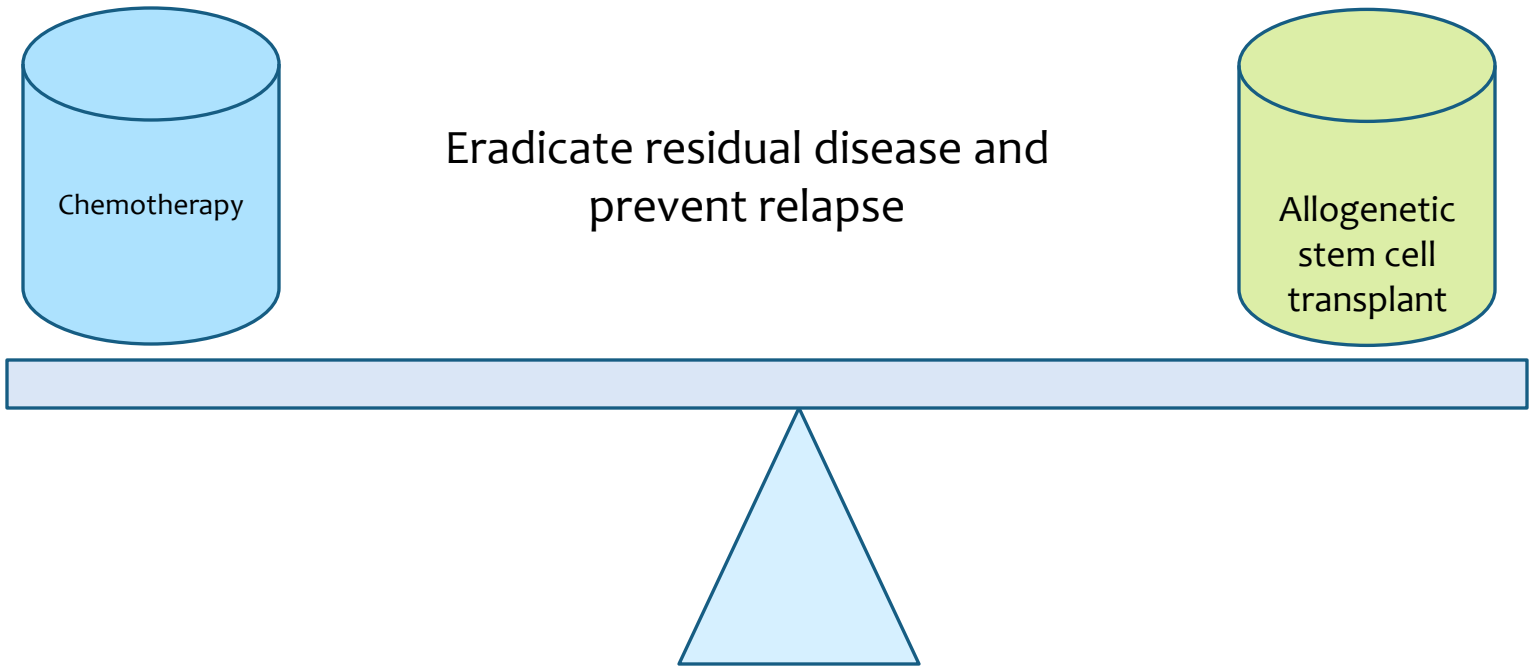
Induction

* '7+3' regimen
  * 7 days of CI cytarabine + 3 days of anthracycline
  * Generally offered to patients with an intermediate to favorable Px and a low risk of tx related mortality
  * Induction regimens using either daunorubicin at 60 or 90 mg/m^2, or idarubicin at 12 mg/m^2 have shown similar rates of CR and survival
  * DNMT3A and KMT2A mutations, which represents a poor prognostic marker, may however benefit from higher doses of daunorubicin.
  * Standard dosing of cytarabine consists of 100–200 mg/m^2 daily administered as a continuous infusion over 7 days. Although studies have shown greater efficacy at higher doses, this added benefit is small and accrued at the cost of increased toxicity
  * FLAG-Ida reasonable alternative with similar CR rates and OS

Consolidation

Cytogenetically favorable AML in first CR

Intermediate-risk and most adverse-risk AML



Risk of TRM should be weighted against the risk of treatment failure or relapse

Consolidation

* Chemo:
  * Intermediate-dose cytarabine (two to four cycles each consisting of six doses at 1.5–3 g/m^2), which has been shown to be as effective as high-dose cytarabine
* Stem Cell Transplant

Hematopoietic stem cell transplant

* Recommended for intermediate to high-risk AML patients when the intent is cure
* Consider patient's fitness, availability of donor, clinical trials, transplant center experience
* Types of donors
  * HLA-matched sibling
  * HLA-matched unrelated
  * HLA-mismatched unrelated
  * HLA-mismatched related (haploidentical)
  * Cord blood

Optimal Treatment Approach in the Elderly

* Overall prognosis highly unsatisfactory
  * More likely to present with an adverse cytogenetic-risk profile
  * Less likely to respond to chemotherapy
  * More susceptible to treatment-related toxicities.

Optimal Treatment Approach in the Elderly

Aggressive

?

Palliative

-Good performance status
-Preserved organ function
-De novo AML
-Favorable to intermediate cytogenetic/molecular prognostic variables

-Marginal performance status
-Secondary AML
-Adverse prognostic variables

AML: Lower Intensity Treatment Options in the Elderly

* Hypomethylating therapy
* Low dose Ara-C
* Clinical trial
* Best supportive care

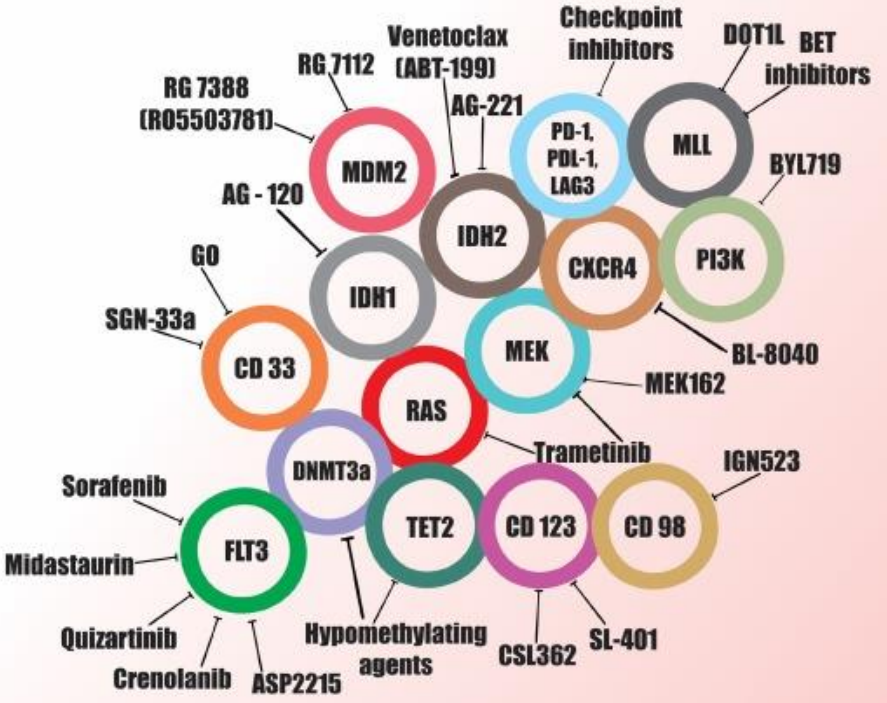
FDA approved Novel Agents

* Midostaurin – Approved 8/2017, for the treatment of adult patients with newly diagnosed *FLT3* mutation-positive AML
* CPX-351 (daunorubicin and cytarabine) – Approved 8/2017, for the treatment of adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
* Enasidenib – Approved 8/2017, for the treatment of adult patients with relapsed or refractory AML with an isocitrate dehydrogenase-2 (*IDH2*) mutation, as detected by an FDA-approved test
* Gemtuzumab ozogamicin – Approved 9/2017, for the treatment of newly diagnosed CD33-positive AML in adults and for treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients ≥2 years

Novel Agents

* FLT3 inhibitors
* IDH1/2 inhibitors
* Monoclonal antibodies
* Clofarabine

* STAT inhibitors
* CAR-T therapy



Conclusions

* AML is generally a disease of older people
* AML is biologically and clinically heterogeneous
* Cytogenetic and molecular aberrations can stratify AML patients into favorable, intermediate, and poor risk groups
* Standard treatment with curative intent includes 7+3, +/- incorporation of targeted agents, +/- HSCT
* Treatment of elderly patients remains a challenge
* Novel strategies

The End