ACUTE MYELOID LEUKEMIA (AML): DIAGNOSIS, TREATMENT AND SIDE EFFECTS MANAGEMENT

BEATING CANCER IS IN OUR BLOOD.

LEUKEMIA & LYMPHOMA SOCIETY

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LEARNING OBJECTIVES

- Describe the various types and subtypes of AML
- Identify tests used to diagnose disease and monitor treatment of AML
- Explain the overarching goals of treatment for the types of AML
- Explain approved and emerging treatment options for AML, including stem cell transplantation, and the role of clinical trials
- Describe the various roles the pharmacist plays in contributing to the management of patients with AML
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments for AML

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Acute Myeloid Leukemia

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Case

- A 68-year-old woman is seen for routine exam and noted to have low platelets with circulating blasts. She is referred to the hematologist who performs a bone marrow biopsy. The results confirm the diagnosis of AML with complex cytogenetics. Molecular mutations reveal IDH2 mutation.
- ➢ What is her prognostic risk classification?
- ➢ What would be the treatment of choice initially?
- ➢ What about treatment if there is a relapse?

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ABC's of Leukemia

- What is Acute Myeloid Leukemia?
- How does AML affect the bone marrow?
- How is the diagnosis made?
- What are the subtypes of AML?

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Diagnosis and Workup of AML

- Bone marrow aspirate and biopsy morphologic evaluation
- Flow-cytometry
- Karyotype analysis (cytogenetics)
- Mutational analysis

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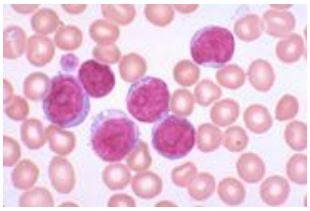
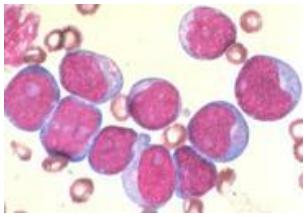
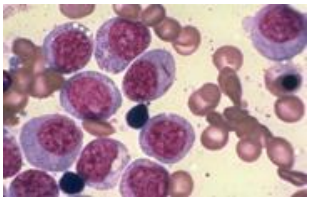
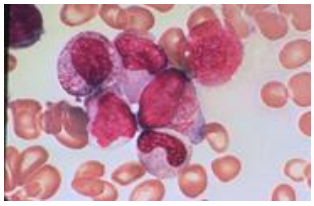
Acute Myeloid Leukemia

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French-American-British (FAB) System

- M0: Myelocytic leukemia without maturation
- M1: Myelocytic leukemia with minimal differentiation
- M2: Myelocytic leukemia with maturation
- M3: Promyelocytic leukemia
- M4: Myelomonocytic leukemia
- M5: Monocytic leukemia
- M6: Erythroleukemia
- M7: Megakaryocytic leukemia

British journal of haematology. 33(4). 451-458.

Acute Myeloid Leukemia

- Most common acute leukemia in adults
- Median age at diagnosis = 67
- Male to female ratio = 5:3
- Associated with chemo +/- radiation exposure, environmental factors, genetic abnormalities, other benign and malignant hematologic *diseases*

http://seer.cancer.gov/statfacts/html/leuks.html

Standard Prognostic Criteria for Non-M3 AML

- Age
- Subtype of AML
- Cytogenetics
- Mutational profiling of AML
- Clinical factors
  - Performance status
  - LDH
  - Creatinine

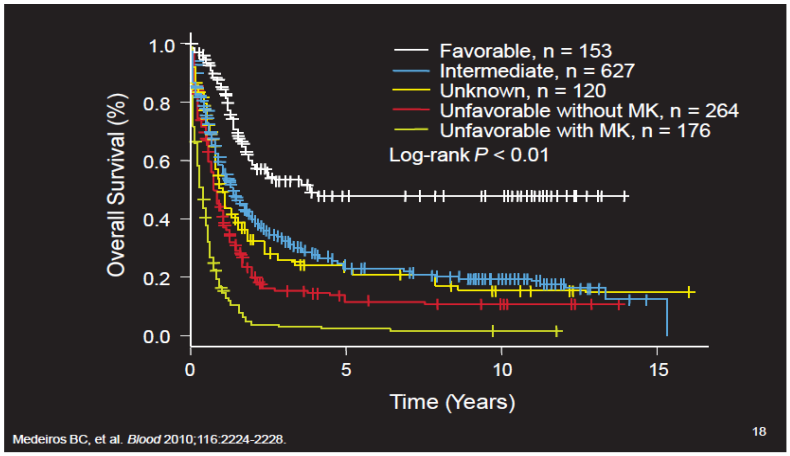
Current opinion in hematology. 12(1). 62-67.

Risk Stratification

Risk Status	Cytogenetics
Better-risk	• t(8;21)(q22;q22) • inv(16)(p13.q22) • t(16;16)(p13.q22) • t(15;17)
Intermediate	• Normal cytogenetics • +8 only • t(3;5) • t(9;11)(p22q23) • Other non-defined
Poor-risk	• Complex karyotype (> 3 abnormalities) • MK+ • -5 / 5q- • -7 / 7q- • Other 11q23 abnormalities, excluding t(9;11) • inv(3)(q21q26.2) • t(3;3)(q21q26.2) • t(6;9) • t(9;22) • 17p abnormalities

Foran JM. *ASH Education Program Book*. 2010:47-55.

Overall Survival According to Revised Cytogenetic Risk



Medeiros BC, et al. *Blood* 2010;116:2224-2228.

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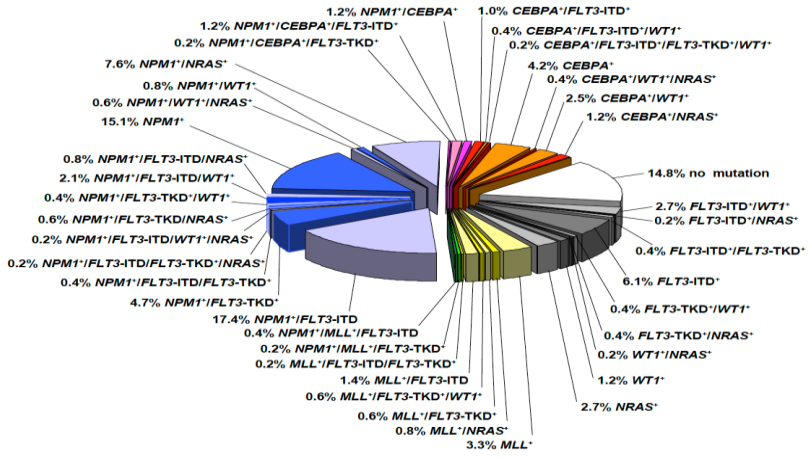
Cytogenetically Normal AML is Highly Heterogeneous



Dohner, H. Blood 2010.

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European Leukemia Net Prognostic Classification of Non- M3 AML

Genetic group	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)
	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-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse†
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	−5 or del(5q); −7; abnl(17p); complex karyotype‡

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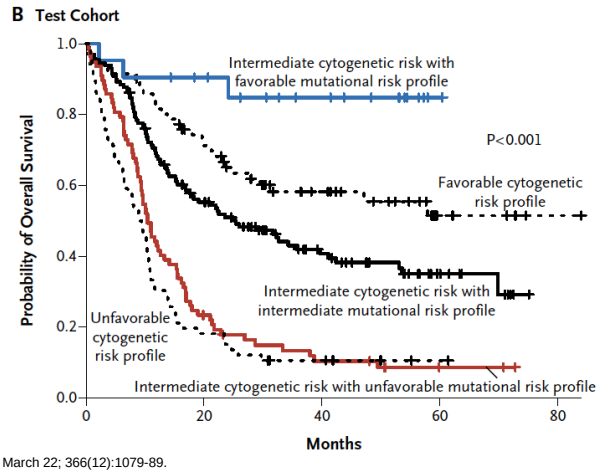
Revised Risk Stratification of Patients with AML on the Basis of Integrated Genetic Analysis



Patel et al. NEJM 2012 March 22; 366(12):1079-89.

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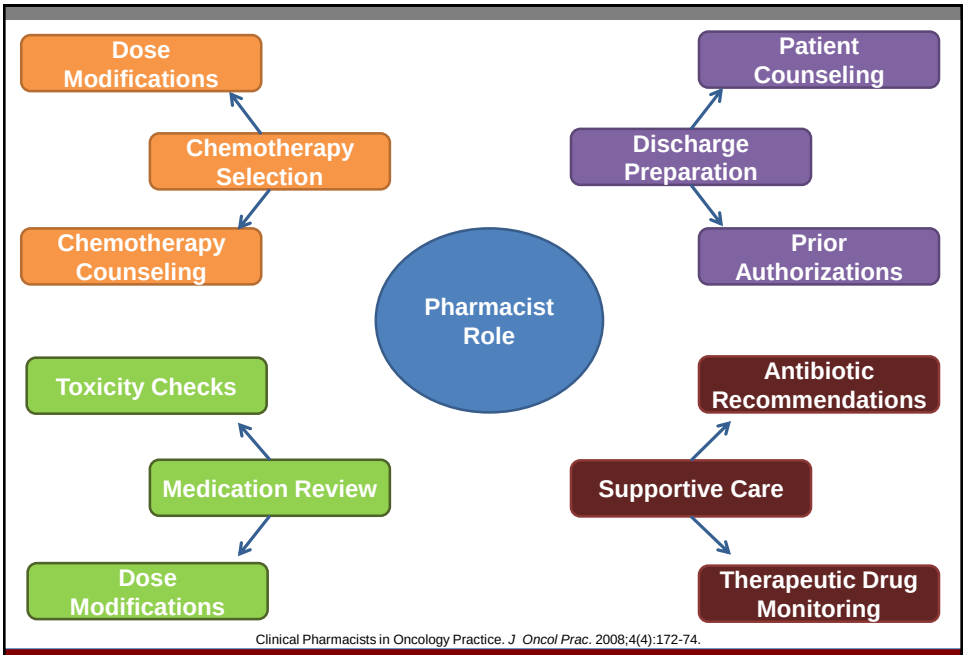
Goals of Treatment in AML

- Young adults (<60 yrs)
  - Induce remission, consolidate with chemotherapy or allo-SCT with a goal to cure
- Fit elderly (>60 yrs)
  - Induce remission, consider allo-SCT in selected patients
- Unfit elderly
  - Induce remission, focus on improving quality-of-life

AML: Currently Effective Modalities of RX

- Cytotoxic chemotherapy (7+3)
- Hypomethylating agents (azacitidine and decitabine)
- Chemo + targeted agents

Leukemia & Lymphoma 54.9 (2013): 2003-2007.
Journal of Clinical Oncology 28.4 (2010): 562-569.
New England Journal of Medicine 361.13 (2009): 1249-1259.



Clinical Pharmacists in Oncology Practice. *J Oncol Prac*. 2008;4(4):172-74.

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Acute Myeloid Leukemia Agents

- Anthracyclines
  - Daunorubicin
  - Idarubicin
  - Daunorubicin/cytarabine (Vyxeos™)
- Antimetabolites
  - Cytarabine
  - Clofarabine
  - Cladribine
  - Fludarabine
- Tyrosine inase Inhibitors
  - Enasidenib (Idhifa®)
  - Midostaurin (Rydapt®)
- Anthracenedione
  - Mitoxantrone
- Podophyllotoxin
  - Etoposide
- Hypomethylating agents
  - Decitabine
  - Azacitidine
- Anti-CD33 antibody
  - Gemtuzumab ozogamicin (Mylotarg™)

Devita, Vincent T. *Cancer Principles and Practice of Oncology*. New York: Wolters Kluwer, 2014. Print.

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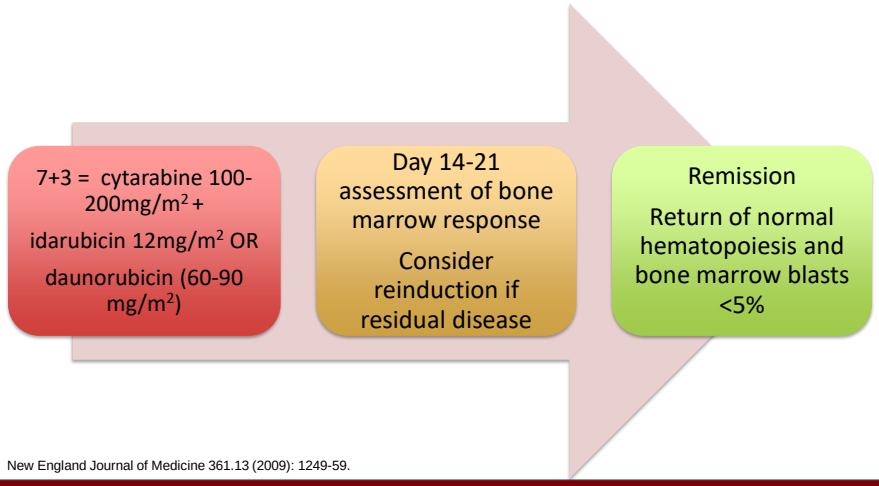
Induction Chemotherapy for Fit AML Patients



New England Journal of Medicine 361.13 (2009): 1249-59.

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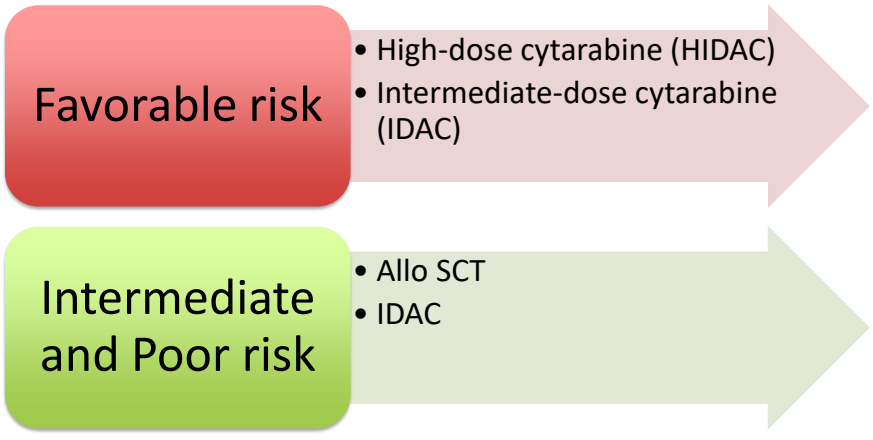
Consolidation Therapy in Fit AML Patients



Journal of Clinical Oncology 31.17 (2013) 2067-69.

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Anthracyclines

- Agents:
  - Daunorubicin, idarubicin
- Mechanism:
  - Anthracyclines to inhibit DNA replication and induce DNA strand breakage through several mechanisms including intercalation of DNA strands, inhibition of DNA polymerase, and topoisomerase II inhibition
- Metabolism:
  - Hepatically metabolized to active and inactive compounds
- Common toxicities:
  - Myelosuppression
  - Gastrointestinal
  - Extravasation
  - Cardiotoxicity

Daunorubicin [package insert]. Bedford, OH: Bedford Laboratories; June 2013.
Idarubicin [package insert]. Schaumburg, IL: APP Pharmaceuticals, LLC; December 2008.

Anthracyclines

- All patients should have an echocardiogram prior to anthracycline administration
  - Caution in patients with LVEF ≤45% or those with ≥10-15% drop from baseline
- Several cardiotoxicity prevention/treatment strategies have been studied, including:
  - Continuous infusion, extended infusion, dose fractionation
  - ACE-I and ARB administration
  - Dexrazoxane administration

Drug	Maximum Lifetime Dose
Daunorubicin	600 mg/m^2
Doxorubicin	450 mg/m^2
Epirubicin	900 mg/m^2
Idarubicin	150 mg/m^2
Mitoxantrone	160 mg/m^2

Volkova M, et al. Anthracycline Cardiotoxicity: Prevalence, Pathogenesis, and Treatment. *Curr Cardiol Rev*. 2011;7(4):214-20.

Cytarabine

- Mechanism:
  - Cytarabine is a pyrimidine analog that is incorporated into DNA chains, as well as inhibits of DNA polymerase, resulting in decreased DNA synthesis and repair
- Metabolism:
  - Metabolized primarily through hepatic pathways, with deoxycytidine kinase and other nucleotide kinases converting cytarabine to azacitidine triphosphate (active) and uracil arabinoside (inactive)
- Common toxicities:
  - Neurotoxicity
  - Gastrointestinal toxicity
  - Hand-foot syndrome
  - Corneal toxicity
  - Hepatic toxicity
  - Cytarabine syndrome (fevers, myalgias, bone pain, chest pain, and rash)

Cytarabine [package insert]. Rockford, Il: Mylan Institutional; December 2013.

25

Cytarabine

- High-dose cytarabine (≥1,000 mg/m^2) is associated with a number of toxicities that require unique prophylaxis and monitoring
  - Conjunctivitis
    - High cytarabine concentrations in the aqueous humor can result in conjunctivitis
    - Patients should receive prophylaxis with dexamethasone 0.1% eye drops, administered as 2 drops in each eye every 6 hours until 48 hours after the last cytarabine dose
  - Neurotoxicity
    - High-dose cytarabine readily crosses the blood-brain barrier, and can result in cerebellar toxicity which presents as difficulty with speech, confusion, tremors, instability, and seizures
    - Risk factors for the development of cerebellar toxicity include: age >50 years, renal impairment, and higher cytarabine doses
    - Patients should be assessed for cerebellar toxicity prior to every dose

Cytarabine [package insert]. Rockford, Il: Mylan Institutional; December 2013.
Chabner, Bruce A. Cancer Chemotherapy and Biotherapy: Principles and Practice. New York: Wolters Kluwer, 2011. Print.

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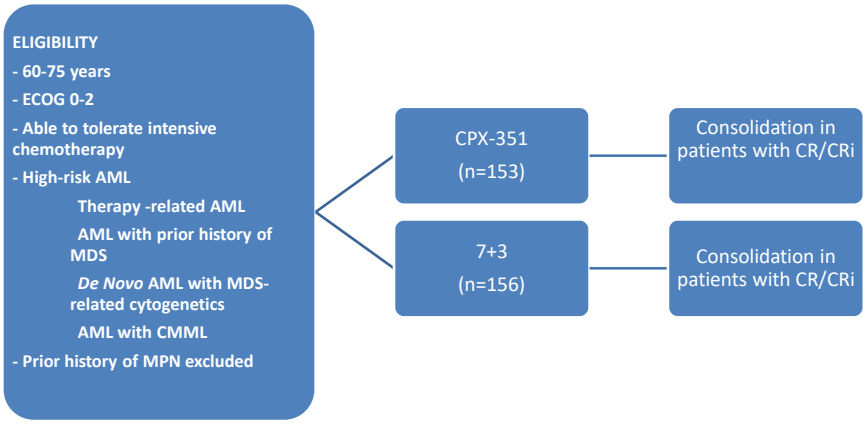
Phase III Trial of CPX-351 (Vyxeos™) in Newly Diagnosed High-Risk (secondary) AML



J Clin Oncol 34, 2016 (suppl; abstr 7000).

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CPX-351 (Vyxeos™) Improves OS in High Risk AML

	CPX-351	7+3
CR	37.3 %*	25.6 %
CR + CRi	47.7 %*	33.3 %
Overall survival	9.56 months*	5.95 months
Percent receiving stem cell transplant	34 %	25 %
60 day mortality	13.7 %*	21.2 %
Grade 3-5 Adverse Events	92 %	91 %
Reduced Ejection Fraction	5%	5%

* Statistically significant

J Clin Oncol 34, 2016 (suppl; abstr 7000).

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Safety

Grade 3-5 Non-hematologic Adverse Events (event frequency ≥ 5%)

MedDRA Preferred Term	CPX-351 (n=153) n (%)	7+3 (n=151) n (%)	All Patients (n=304) n (%)
Febrile Neutropenia	104 (68)	107 (71)	211 (69)
Pneumonia	30 (20)	22 (15)	52 (17)
Hypoxia	20 (13)	23 (15)	43 (14)
Sepsis	14 (9)	11 (7)	25 (8)
Hypertension	16 (10)	8 (5)	24 (8)
Respiratory Failure	11 (7)	10 (7)	21 (7)
Fatigue	11 (7)	9 (6)	20 (7)
Bacteraemia	15 (10)	3 (2)	18 (6)
Ejection Fraction Decreased	8 (5)	8 (5)	16 (5)

PRESENTED AT: ASCO ANNUAL MEETING '16

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Presented By Jeffrey Lancet at 2016 ASCO Annual Meeting.

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Daunorubicin/Cytarabine (Vyxeos™)

- Formulation:
  - Compound consisting of cytarabine:daunorubicin in a fixed 5:1 molar ratio encapsulated in a lipid formulation
- Mechanism/metabolism:
  - Liposomes are taken up by bone marrow cells, and undergo degradation following internalization, releasing the active chemotherapeutic agents within the cells
- Common toxicities:
  - Febrile neutropenia
  - Pneumonia
  - Hypoxia
  - Sepsis
  - Bacteremia
  - Fatigue
  - Reduced ejection fraction

Vyxeos (daunorubicin and cytarabine [liposomal]) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals Inc; August 2017.

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Daunorubicin/Cytarabine (Vyxeos™)

US Boxed Warning

Daunorubicin/cytarabine (liposomal) has different dosage recommendations than daunorubicin (conventional), cytarabine (conventional), daunorubicin (liposomal), and cytarabine (liposomal). Verify drug name and dose prior to preparation and administration to avoid dosing errors.

Regimen	Dose	Schedule
7+3 • Cytarabine • Daunorubicin	 100 mg/m^2 60 – 90 mg/m^2	 Induction: days 1 – 7 Induction: days 1 – 3
Vyxeos™ • Daunorubicin/Cytarabine*	44 mg/m^2 and 100 mg/m^2	Induction: days 1, 3, 5 Reinduction: days 1, 3

*Vyxeos™ dosing differs when being administered during consolidation

Cytarabine (prescribing information). Rockford, Il: Mylan Institutional; December 2013.
Daunorubicin [prescribing information]. Bedford, OH: Bedford Laboratories; June 2013.
Vyxeos (daunorubicin and cytarabine [liposomal]) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals Inc; August 2017.

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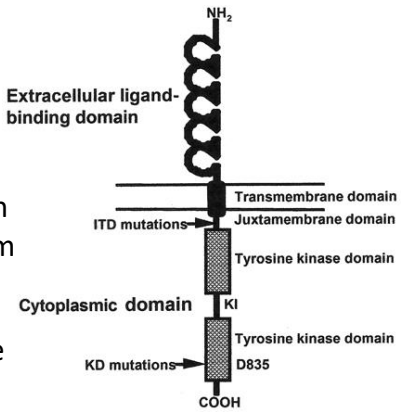
FLT3-ITD

- FML-like tyrosine kinase 3 internal tandem duplication
- Mutated in about one-third of AML patients
- FLT3 is a receptor tyrosine kinase with important roles in hematopoietic stem cell survival and proliferation
- Associated with an aggressive disease phenotype (increased relapse rates and worse survival)



D. Small ASH Education Book 2006.

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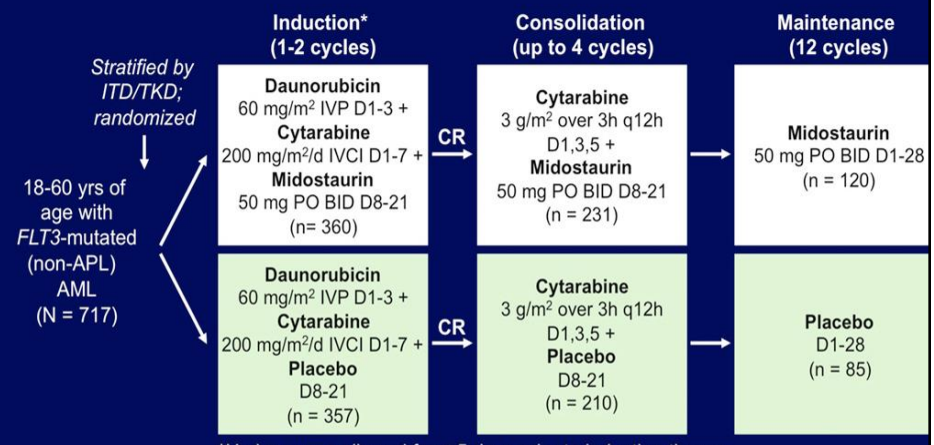
RATIFY: Study Design



*Hydroxyurea allowed for ≤ 5 days prior to induction therapy.

- Double-blind, placebo-controlled, randomized phase III study
  - Primary endpoint: OS (not censored for SCT)
  - Secondary endpoint: EFS

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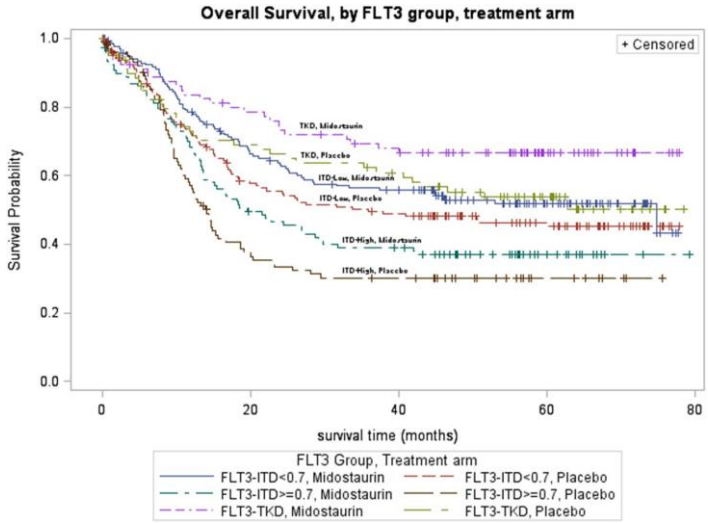
Midostaurin Improves Survival in All FLT3 Mutated AML



Richard M. Stone et al. Blood 2015;126:6.

34

Overall Safety Profile

- No statistically significant differences were observed in the overall rate of grade 3 or higher hematologic and non-hematologic adverse events (AEs) in the midostaurin versus the placebo group.
- The most frequent all-grade AEs were febrile neutropenia, nausea, exfoliative dermatitis, vomiting, headache, and petechiae.
- No difference in treatment-related deaths observed between groups

Midostaurin

- Mechanism:
  - Inihibits wild-type and mutant FLT3 (ITD/TKD), as well as KIT, PDGFRα/β, VEGFR2, and protein kinase C
- Metabolism:
  - Undergoes hepatic metabolism via CYP3A4 to active metabolites
- Common Toxicities
  - Febrile neutropenia
  - Nausea/vomiting
  - Mucositis
  - Headaches
  - Muscluloskeletal pain
  - Hyperglycemia
  - Respiratory tract infections
  - Pulmonary toxicities

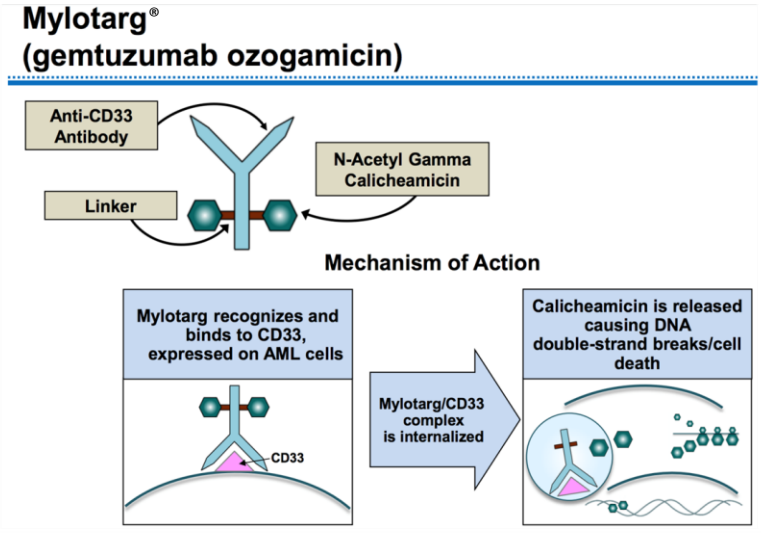
Rydapt (midostaurin) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2017.

Midostaurin

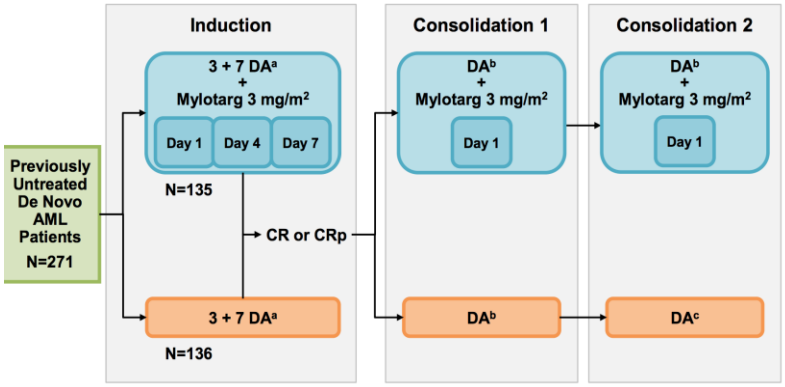
- Administration:
  - Should be administered at approximately 12 hour intervals, and taken with food
- Pharmacokinetics:
  - Half-life of parent drug is 21 hours, but metabolites have half-lives ranging from 32 (CGP62221) – 482 (CGP52421) hours
- Drug-drug interactions:
  - Major substrate of CYP3A4
    - Should avoid any strong CYP3A4 inhibitors
  - Inhibits OATP1A1/SCLO1A1
  - Induces MRP2

Rydapt (midostaurin) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2017.

Gemtuzumab Ozogamicin



ALFA-0701 (MF3): Phase 3 Study Design



Blood 2014 124:376.

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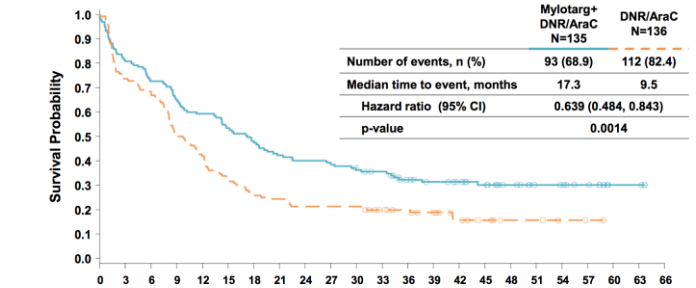
Gemtuzumab Ozogamicin Increases Event-Free Survival

ALFA-0701: Event-Free Survival – Longer Follow-Up



Number at Risk																						
Mylotarg+ DNR/AraC	135	109	98	88	80	72	65	57	54	53	48	45	36	32	29	25	19	14	13	10	3	3	0
DNR/AraC	136	100	93	69	57	44	35	33	29	29	29	23	19	16	10	7	4	4	2	1	0		

Blood 2014 124:376.

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Gemtuzumab Ozogamicin

- Mechanism:
  - Humanized anti-CD33 monoclonal antibody-drug conjugate, with a cytotoxic calicheamicin derivative attached
- Metabolism:
  - Undergoes non-enzymatic reduction of disulfide moiety
- Common toxicities:
  - Fever
  - Nausea/vomiting
  - Thrombocytopenia
  - Stomatitis
  - Constipation
  - Liver function abnormalities (hepatic veno-occlusive disease)

Mylotarg (gemtuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; April 2018.

Gemtuzumab Ozogamicin

US Boxed Warning

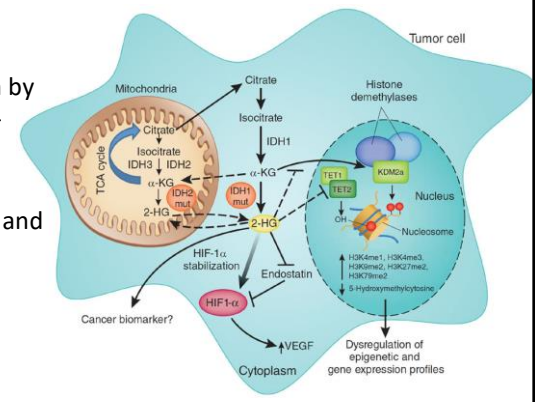
Hepatotoxicity, including severe or fatal hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), has been reported in association with the use of gemtuzumab ozogamicin as a single agent and as part of a combination chemotherapy regimen. Monitor frequently for signs and symptoms of VOD after treatment with gemtuzumab ozogamicin.

Note: Median onset occurs 9 days after drug administration, but occurred at a range of 2 to 298 days. The risk is highest in patients receiving higher gemtuzumab doses, those with moderate to severe baseline hepatic impairment, in patients receiving gemtuzumab following stem cell transplant, and patients undergoing stem cell transplant after receiving gemtuzumab.

Mylotarg (gemtuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; April 2018.

Mutations in Metabolic Enzyme Pathways: IDH1 and IDH2

- First identified in gliomas
- Alter physiologic enzyme function by converting α-ketoglutarate into 2-hydroxyglutarate, an oncogenic metabolite
- Associated with NPM1 mutations and predict worse outcome



Nature Medicine 17, 291–293 (2011).

43

AG-221 (Enasidenib) in IDH2-Mutated AML

- 198 patients treated on phase I and II study
- Median age 69 years
- 70% patients had relapsed/refractory disease, 64% had more than 2 treatment regimens
- Median treatment duration 6 months
- Highest dose 450 mg
- MTD not reached
- Response rate seen in all types of IDH2 mutation
- Among responders, ANC increased by 1 month of therapy

SIDE EFFECTS

- Indirect hyperbilirubinemia (19%)
- Nausea (18%)
- Leucocytosis (treatment-related N=7)
- Differentiation syndrome?

Stein et al Blood, 126(23), 323.

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Response

	RR-AML (n = 159)	Untreated AML (n = 24)	MDS (n = 14)	All (N = 209)
Overall Response (CR, CRp, CRi, mCR, PR)	59 (37%)	10 (42%)	7 (50%)	79 (38%)
CR	29 (18%)	4 (17%)	3 (21%)	37 (18%)
CRp	1 (1%)	1 (4%)	1 (7%)	3 (1%)
CRi	3 (2%)	0	0	3 (1%)
mCR	9 (6%)	1 (4%)	3 (21%)	14 (7%)
PR	17 (11%)	4 (17%)	0	22 (11%)
SD	72 (45%)	9 (38%)	6 (43%)	96 (46%)
PD	10 (6%)	1 (4%)	0	11 (5%)
Not evaluable	18 (11%)	4 (17%)	1 (7%)	23 (11%)

Memorial Sloan Kettering Cancer Center

Presented By Eytan Stein at 2016 ASCO Annual Meeting.

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Enasidenib

- Mechanism:
  - Targets mutant and wild-type IDH2 (targets mutant IDH2 at 40-fold lower concentrations), reducing abnormal histone hypermethylation and restoring normal myeloid differentiation
- Metabolism:
  - Undergoes hepatic metabolism via CYP and UGT
- Common toxicities:
  - Nausea/vomiting
  - Diarrhea
  - Increased bilirubin
  - Decreased appetite

Idhifa (enasidenib) [prescribing information]. Summit, NJ: Celgene Corporation; August 2017.

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Enasidenib

US Boxed Warning

Patients treated with enasidenib have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

Note: Can occur with or without hyperleukocytosis, and the onset may be variable ranging from a few days after initiation to up to 5 months following initiation of therapy. Standard therapy includes oral or intravenous corticosteroids.

Idhifa (enasidenib) [prescribing information]. Summit, NJ: Celgene Corporation; August 2017.

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Enasidenib

- Administration:
  - Take at approximately the same time each day, without regard to food, with a full glass of water
- Drug-drug interactions:
  - Extensive CYP substrate
    - CYP1A2, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4
  - Extensive UGT substrate
    - UGT1A1, UGT1A3, UGT1A4, UGT1A9, UGT2B15, UGT2B7

Idhifa (enasidenib) [prescribing information]. Summit, NJ: Celgene Corporation; August 2017.

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Elderly AML: Treatment Options

- Palliative care
- Traditional induction chemotherapy
- Low-intensity Rx – Hypomethylating agents and low-dose cytarabine
- Targeted treatments and clinical trials

Leukemia & Lymphoma 54.9 (2013): 2003-2007.
Journal of Clinical Oncology 28.4 (2010): 562-569.

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Low-Intensity Options in AML

- Can be administered as outpatient
- Relative lack of non-hematologic side effects and well tolerated
- Take several cycles to respond
- Effective in achieving CR and improving survival compared to supportive care alone

Leukemia & Lymphoma54.9 (2013): 2003-2007.
Journal of Clinical Oncology 28.4 (2010): 562-569.

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Hypomethylating Agents

- Agents:
  - Decitabine, azacitidine
- Mechanism:
  - Acts to inhibit methyltransferase, resulting in hypomethylation of DNA, causing differentiation and apoptosis of malignant cells, and restoring normal gene differentiation and proliferation
- Metabolism:
  - Decitabine undergoes deamination by cytidine deaminase; azacitidine undergoes hydrolysis to metabolites
- Toxicities:
  - Myelosuppression
  - Gastrointestinal (constipation)
  - Stomatitis
  - Lethargy

Note: azacitidine carries a moderate emetic risk and requires prophylactic antiemetics, while decitabine only carries minimal emetic risk.

Azacitidine [package insert]. Summit, NJ: Celgene Corporation; January 2014.
Decitabine [package insert]. Rockville, MD: Otsuka America Pharmaceutical; October 2014.

Acute Promyelocytic Leukemia (APL)

- Frequently presents in young patients
- Very high risk of bleeding
- Very high cure rates if patients survive the bleeding risk
- Caused by translocation (15;17) fusing PML-RAR-alpha genes leading to block in differentiation

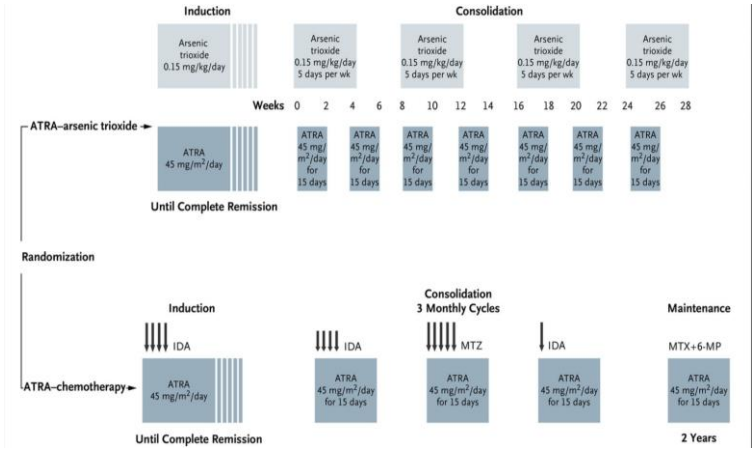
Blood. 85(10). 2643-2653.
Oncogene 6.7 (1991): 1285-1292.

APL

- All Trans Retinoic Acid (ATRA) is the most successful targeted treatment in AML
- ATRA stops the differentiation block in the APL cells leading to differentiation of blasts to normal cells
- Treatment of ATRA is associated with differentiation syndrome
- Early recognition and treatment of differentiation syndrome is critical
- Differentiation syndrome is characterized by leukocytosis, fluid retention, weight gain, effusions, fever, and shortness of breath
- Treatment with steroids

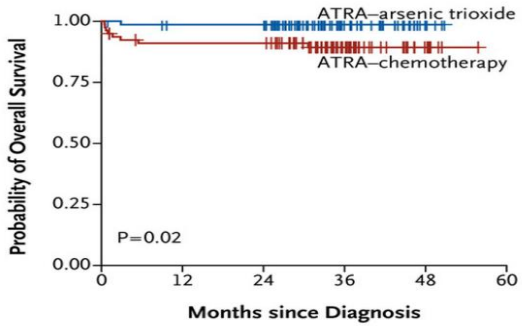
Blood 113.4 (2009): 775-783.

Treatment of Low-Risk APL



Lo Coco et al *New England Journal of Medicine* 369.2 (2013): 111-121.

Survival in Low-Risk APL



No. at Risk

ATRA–arsenic trioxide	77	73	73	29	5
ATRA–chemotherapy	79	69	69	29	7

Lo Coco et al *New England Journal of Medicine* 369.2 (2013): 111-121.

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Toxicity Profile of ATRA and Arsenic

Toxicity	Percentage
QTc prolongation	15.6%
Hepatotoxicity	63.2%
GI toxicity	4.4%
Hematological toxicity- Thrombocytopenia	59%
Hematological toxicity- neutropenia	46%

Lo Coco et al *New England Journal of Medicine* 369.2 (2013): 111-121.

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Long-Term Monitoring of Patients with AML

- Monitoring for relapse
- Monitoring for long-term toxicity
  - Secondary leukemia
  - Transplant complications
  - Cardiotoxicity
  - Fertility issues

Hematology/oncology and stem cell therapy. 5.1 (2012): 1-30.

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Financial Assistance Programs

- The Leukemia and Lymphoma Society offers patients financial guidance
  - Please visit www.LLS.org/Financesor call 1-800-955-4572
- Midostaurin
  - Rydapt® NOW
    - Can supply a free 14-day supply of midostaurin for patients facing delays in acquisition due to financial hardship
  - Novartis Oncology Universal Co-Pay Card Program
    - Can lower monthly co-pay to $10 for patients with commercial insurance, up to a maximum $15,000 annual benefit cap
- Enasidenib
  - Celgene Commercial Co-Pay Program
    - Can reduce monthly co-pay to $25, for patients with commercial insurance
  - Celgene Patient Assistance Program
    - Can provide financial assistance to patients with no or inadequate insurance that meet certain income & financial qualifications

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Case Revisited..

- A 68-year-old woman is seen for routine exam and noted to have low platelets with circulating blasts. She is referred to the hematologist who performs a bone marrow biopsy. The results confirm the diagnosis of AML with complex cytogenetics. Molecular mutations reveal IDH2 mutation.
- ➢ What is her prognostic risk classification?
- ➢ What would be the treatment of choice initially?
- ➢ What about treatment if there is a relapse?

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Landscape in Treatment of AML

Young patients	Fit elderly	Unfit elderly
FLT3-negative- 7+3	High-risk AML- CPX-351	Hypomethylating agents
FLT3-positive- midostaurin + 7+3	Not high-risk- 7+3	Low-dose cytarabine
		IDH2-mutated (relapsed disease)

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Emerging and Promising Agents for the Treatment of AML

Agent	Mechanism of action	Suggested patient population
Guadecitabine	Hypomethylating agent resistant to deamination	Unfit for intensive chemotherapy
Venetoclax	Bcl2 inhibitor	Newly diagnosed unfit for induction patients
Volasertib	Novel PLK1 inhibitor	Being explored as a combination with hypomethylating and traditional induction
Quizartinib	FLT3 inhibitor	FLT3 + AML
Crenolanib	FLT3 inhibitor with activity against TKD-resistance mutation	FLT3-ITD or FLT3-TKD
ASP-2215	FLT3 inhibitor with activity against TKD-resistance mutation	FLT3-ITD or FLT3-TKD
AG-120	IDH1 inhibitor	IDH1 mutated
EPZ-5676	DOT1L inhibitor	MLL rearranged
OTX-015	BET inhibitor	Ongoing investigation
Pracinostat	HDAC inhibitor	Ongoing investigation

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The Weill Cornell/NYP Leukemia Program

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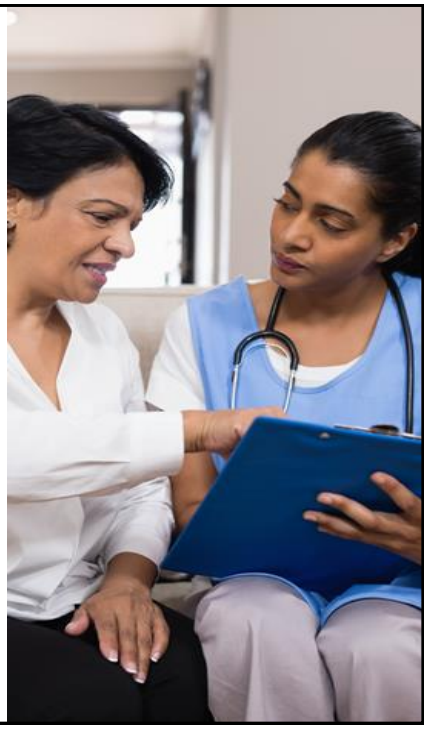
The Nurse's, Nurse Practitioner's, and Social Worker's Roles in the Treatment of Patients With AML



Ayelet Nelson, RN, LMSW, ANP-BC
Leukemia Outpatient Nurse Practitioner
Weill Cornell Medicine
New York, NY

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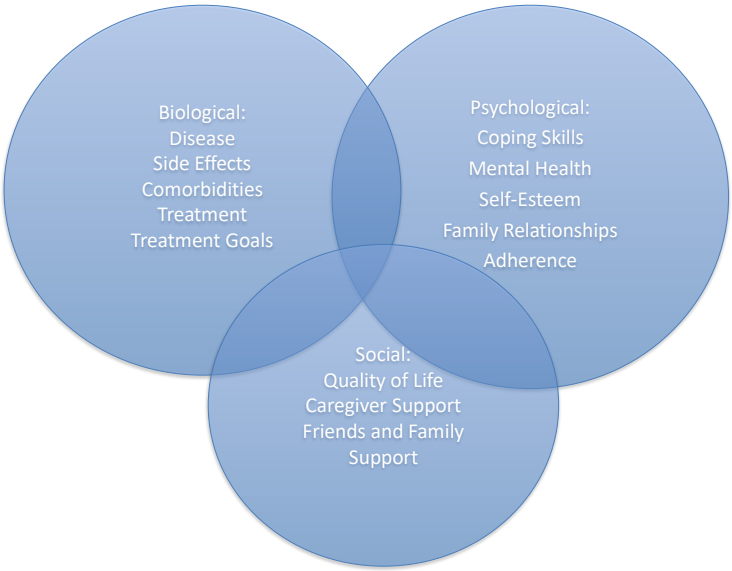
Biopsychosocial Approach to Care



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Biopsychosocial Approach to Care

- Biological:
  - Explanation of disease in terms a patient can understand and digest (at diagnosis and throughout treatment course)
  - Elaborating on treatment rationale
  - Education around treatment and side effects

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Biopsychosocial Approach to Care

- Biological:
  - Management of side effects from disease and treatment
  - Identifying new or changing symptoms
  - Ongoing explanation of blood tests, radiology studies, pathology/bone marrow reports
  - Perform bone marrow biopsies (NP)

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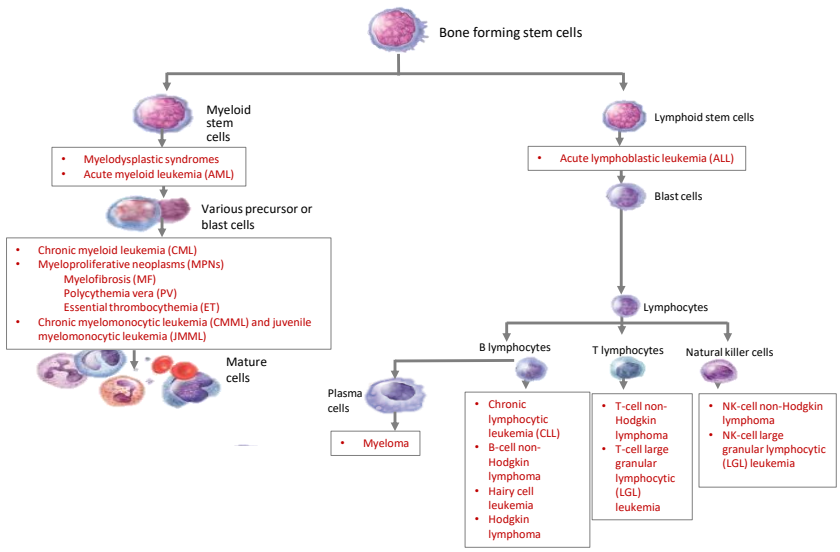
Blood Cancers Can Develop in Many Different Places Within Normal Blood Cell Formation.
The type of blood cancer that results has to do with where normal cell development is blocked. This picture shows the cell types where different blood cancers arise.



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AML 101: Understanding the Routine Visit

- What is a compete blood count (CBC)?
- When do we typically give transfusions?
- What is a manual differential?
  - Neutrophils
  - Blasts

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Common Side Effects of AML and Treatment of AML

- Myelosuppression (neutropenia, anemia, thrombocytopenia)
- Fatigue
- GI toxicities
- Poor appetite
- Infertility

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Neutropenia

- Provide education related to signs and symptoms of infection
- When to call the office; when to go immediately to the emergency room
- Prophylactic antimicrobials (NP)
- Neutropenic precautions, e.g., good hand-washing, avoiding sick contacts
- ?Growth Factors (NP)

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Anemia

- Provide education regarding signs and symptoms of anemia
- Fatigue most commonly reported symptom in patients with anemia
- Identification of when transfusion is indicated
- Transfusion complications: infusion reaction, development of antibodies

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Thrombocytopenia

- Provide education regarding signs and symptoms of bleeding, lifestyle changes
- Identification of when transfusion is indicated
- Transfusion complications: infusion reaction, development of antibodies

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Fatigue

- One of the most difficult side effects to treat
  - Blood is not always the answer
  - Encouraging light exercise – i.e., walking!
  - Listening to your body

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Gastrointestinal Toxicity

- Nausea: Identify and treat EARLY!
  - Side effect of specific treatments
  - Choosing an antiemetic (NP)
- Constipation: Identify and treat EARLY!
  - Side effect of specific treatments
  - Prevention vs. treatment
- Diarrhea: Identify and treat EARLY!
  - Side effect of specific treatments
  - Electrolyte imbalances
  - Test for infectious process before treating

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Poor Appetite

- Weight loss is common with AML therapy
  - Identify if it is poor appetite or nausea
  - High calorie foods
  - High protein foods
  - Maximizing every bite
  - Grazing
  - Nutrition consult
  - Medical marijuana
  - Mirtazapine

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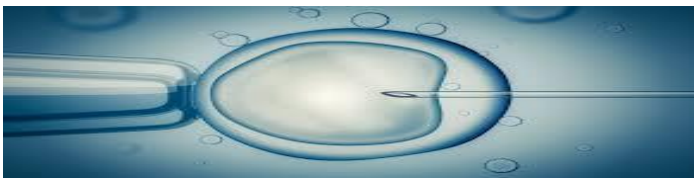
Infertility

- Important to address early-at diagnosis!
  - Nurse/NP has an important role in starting this discussion and revisiting this
  - Men: Cryopreservation of semen
  - Women: Early referral to a reproductive endocrinologist for discussion at diagnosis of fertility preservation or long-term plan for fertility



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Treatment Goals

- Clarification of goals of therapy
- Ongoing discussion of disease status and treatment updates
- Quality of life
- Collaboration with clinical trial staff
- End of life conversations

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Micromanagement: Ongoing Goals of Therapy

- Maintenance of counts
- Improvement in counts
- Transfusion independence
- Minimize/manage toxicities
- Improve/maintain quality of life
- Stabilize disease vs. cure

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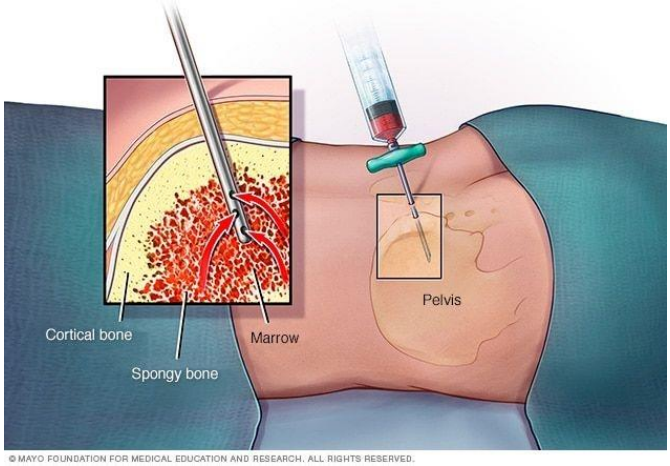
Bone Marrow Biopsy



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Biopsychosocial Approach to Care

- Psychological:
  - Act as a confidant for patients and liaison to multidisciplinary team
  - Emotional support for patients and their caregivers
  - Identifying stressors and assisting with management
  - Mental health referrals
  - Addressing adherence and collaborating with patients to increase adherence to medications (including oral chemotherapy drugs as well as supportive medications)

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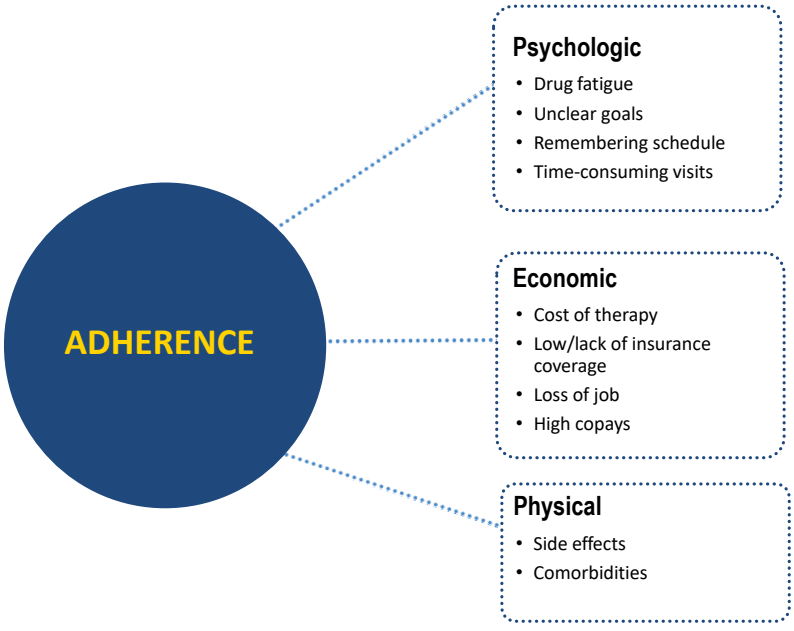

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Biopsychosocial Approach to Care

- Social:
  - Loss of job, autonomy, daily routine
  - Change of role in family unit and in other arenas
  - Appropriate referrals to organizations for support
  - Referral to social work

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The Social Worker's Role

- Establish relationship with social worker early on (at diagnosis!)
  - Counseling for patient and support network
  - Access to durable medical equipment to assist with ADLs
  - Referral to appropriate support groups, organizations
  - Financial assistance

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Tying It All Together

- Reinforce patient and caregiver teaching with each visit
- Assess patient preferences for teaching (e.g, paper, verbal discussion, webinar)
- Ensure patient goals are in line with therapy prescribed; address treatment adherence
- Encourage questions; suggest writing down questions before visit, so patients don't forget

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Summary

- Nurses, Nurse Practitioners, and Social Workers are in the unique role of addressing the multifaceted experience of being treated for AML
- Education is a key responsibility and piece of the relationship
- Management of side effects both from disease and treatment is a priority
- Address ongoing treatment and treatment goals with patients and caregivers
- Serve as a liaison to other members of the multidisciplinary team to ensure holistic approach to care

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THANK YOU

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ACUTE MYELOID LEUKEMIA: DIAGNOSIS, TREATMENT, AND SIDE EFFECTS MANAGEMENT

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- Online & In-person **free CME & CE courses** – www.LLS.org/CE
- **New** Podcast series for healthcare professionals – www.LLS.org/CE

Listen as we speak with experts about diagnosis, treatment and survivorship to educate HCPs treating with blood cancer.

Clinical Trials and Research

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- Research: finding cures and bridging the gap between academic discovery & drug development – www.LLS.org/Research

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ACUTE MYELOID LEUKEMIA: DIAGNOSIS, TREATMENT, AND SIDE EFFECTS MANAGEMENT

Resources for Your Patients

- AML Specific Resources – www.LLS.org/AML
- Booklets on AML and related topics – www.LLS.org/Booklets
- Telephone/Web Education Programs – www.LLS.org/Programs
- Videos – www.LLS.org/Educationvideos
- Podcasts – www.LLS.org/LLS-podcast

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ACUTE MYELOID LEUKEMIA: DIAGNOSIS, TREATMENT, AND SIDE EFFECTS MANAGEMENT

Resources for Your Patients

Information Specialists – www.LLS.org/IRC

Assist through treatment, financial & social challenges, and give accurate treatment and support information. HCPs can also order free materials to distribute to patients.

Clinical Trial Support Center – www.LLS.org/CTSC

Patients & caregivers work one-on-one with **clinical trial specialists who are RNs** with expertise in blood cancers. RNs will personally assist through the clinical trial process, providing an **additional resource to your HCP team**.

- Phone: (800) 955-4572, M-F, 9 am to 9 pm ET
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/InformationSpecialists

Additional Support Resources – www.LLS.org/Support

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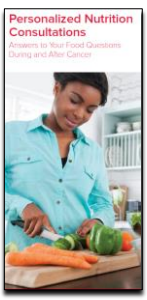
ACUTE MYELOID LEUKEMIA: DIAGNOSIS, TREATMENT, AND SIDE EFFECTS MANAGEMENT

Resources for Your Patients

- One-On-One Nutrition Consultations (PearlPoint)
- LLS Community (social media platform)
- Patti Robinson Kaufman First Connection Program (peer-to-peer)



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