Acute Myeloid Leukemia (AML): Finally Making Progress?

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Disclosures

- Honoraria (ended 12/2017): Celgene, Tolero
- Research support: Merck, Takeda Millennium, Tolero

Objectives

- To discuss pathogenesis/etiology of AML
- To discuss diagnostic testing in AML
- To discuss management of AML in both younger & older patient populations highlighting recent drug approvals
- To discuss novel concepts and investigational agents for treatment of AML

Case

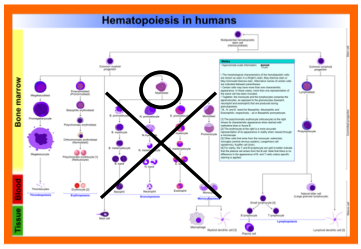
- 67 yo M with past medical history significant for Stage I Squamous Cell Carcinoma of Oropharynx in 2015, s/p Cisplatin + XRT, with no evidence of recurrence, presents with progressive fatigue, chest tightness and found to have pancytopenia with WBC = $1.3x10^9$/L, Hb = 7.8 g/dL, and platelet count = $69x10^9$/L. A bone marrow biopsy is performed revealing 20% blasts by manual aspirate differential with multilineage dysplasia. Cytogenetics reveal a highly complex karyotype and NGS mutational testing reveals TP53 mutation. The patient otherwise has an ECOG PS = 0 and is healthy with minimal other comorbidities.

Question 1

What is the next step in the management of this patient?

A) Refer directly for allogeneic stem cell transplant
B) 7+3 induction chemotherapy
C) CPX-351
D) Azacitidine
E) 7+3 + Midostaurin

What is AML?



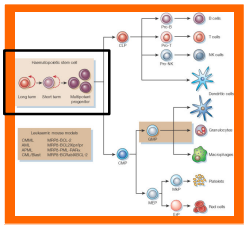
Adapted from commons.Wikimedia.org/wiki/file:hematopoiesis_(human)_diagram.png

- Clonal proliferation of myeloid precursors (i.e. myeloblasts)
  - Reduced capacity for differentiation
  - Reduced capacity for cell death-> uncontrolled proliferation

Pathogenesis of AML

- Stem Cell Hypothesis- AML arises from early hematopoietic progenitor/stem cell

- Two-Hit Hypothesis
  - Class 1 Mutations
    - Proliferative advantage
    - Ex: FLT3, NPM1, C-KIT
  - Class 2 Mutations
    - Impair hematopoietic diff.
    - Ex: CEBPA

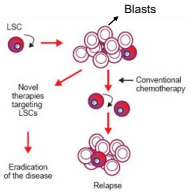


Reya, Nature 2001

Pathogenesis of AML

- Stem Cell Hypothesis- AML arises from early hematopoietic progenitor/stem cell- LSC

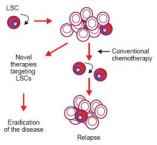
- Stem cells- 3 basic properties
  - Not cell cycle-dependent
  - Capable of self-renewal
  - Produce committed progenitor cells
- Stem cells inherently chemoresistant
- Origin of LSC likely dictates prognosis and drug resistance



Cancer Control 2004- H. Lee Moffitt Cancer Center and Research Institute

How To Cure AML?

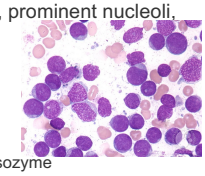
- Holy grail of AML = Cure
- Working hypothesis is that all (or most) AML's arise from a LSC
- The more primitive LSC- harder to eradicate -> refractory and/or relapse
- Genetic features of AML provide a clue for how primitive AML is



Cancer Control 2004- H. Lee Moffitt Cancer Center and Research Institute

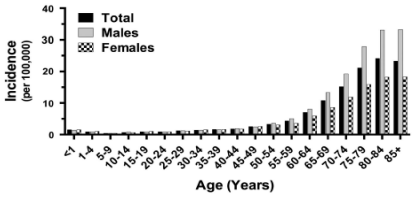
Pathology of AML

- Diagnosis: ≥20% myeloblasts in PB or BM
  - Blast % irrelevant in CBF AML [t(8;21); inv(16)] and APL
- Morphology: Smooth chromatin, prominent nucleoli, Auer Rods
- Immunophenotype:
  - Myeloid antigens:
    - MPO, CD13, CD33, CD15
  - Monocytic antigens:
    - NSE, CD11c, CD14, CD64, Lysozyme
  - Blast markers:
    - CD34, CD117



Maslak P, ASH Image Bank

Epidemiology of AML

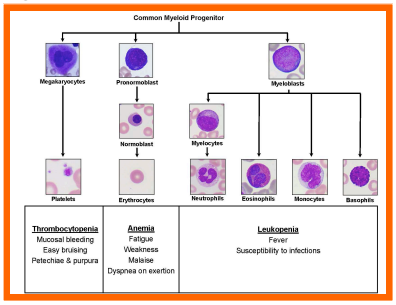


- 18,000 new cases of AML/year
  - > 10,000 deaths/year
- Median age- 67-68 years
  - All ages can be affected

SEER Data, Walter, Leukemia 2015

Clinical Presentation

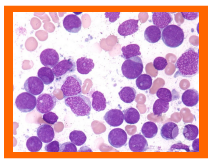
- Rapid onset of symptoms over 1-7 days, can be more protracted in MDS-> AML



Duncan D et al., Acute Leukemia Textbook 2017.

Diagnosis

- Bone marrow biopsy and morphology
- If circulating blasts-> can make dx by flow cytometry
- Myeloblasts ≥20% in bone marrow or blood
- Cytogenetics and molecular markers- Critical!



Maslak P, ASH Image Bank

Classification/Prognostication

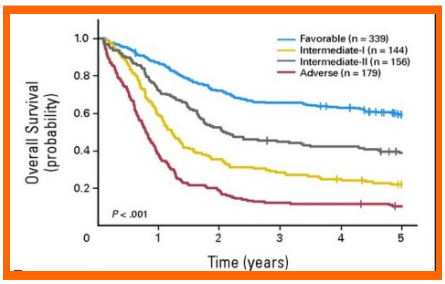
- FAB Classification outdated (M0-M7)
- Genetic information critical for prognostication
  - It's really all about the chromosomes!
- European LeukemiaNet (2010)- 4 risk groups

ELN Risk	Cytogenetic/Molecular	Incidence-Younger pts	Incidence-Older pts
Favorable	• t(8;21); inv(16); t(16;16) • Normal karyotype + NPM1 mut. w/o FLT3-ITD • Normal karyotype + CEBPA double mut.	41%	20%
Intermediate-1	• Normal karyotype + FLT3-ITD • Normal karyotype and NPM1/FLT3 wt	18%	19%
Intermediate-2	• t(9;11) and all other abn.	19%	30%
Adverse	• Inv(3); t(3;3); t(6;9); t(v;11); -5; del(5q); -7; abnl(17p); complex	22%	31%

Dohner, Blood 2010; Mrozek, J Clin Oncol 2012

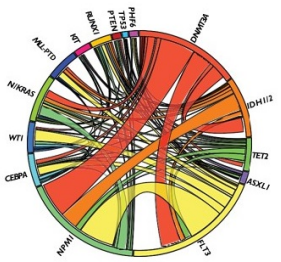
Do Risk Groups Matter?

- Risk groups validated to predict outcome



Mrozek, J Clin Oncol 2012

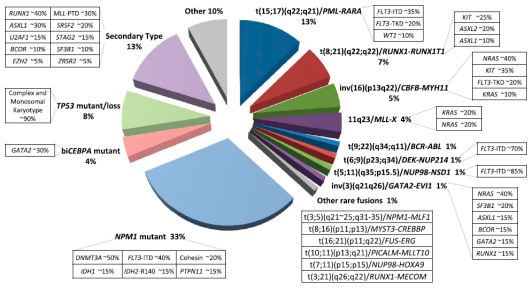
AML is a Heterogeneous Disease



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	5
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

Patel, NEJM 2012

Complexity of Molecular Mutations in AML



Grimwade, Blood 2016

11 Genomic Classes of AML

Table 1. Proposed Genomic Classification of Acute Myeloid Leukemia (AML).

Genomic Subgroup	Frequency in the Study Cohort (N = 1540)	Most Frequently Mutated Genes*
	no. of patients (%)	*gene (%)*
AML with *NPM1* mutation	418 (27)	**NPM1** (100), *DNMT3A* (54), *FLT3*^{ITD} (39), *NRAS* (19), *TET2* (16), *PTPN11* (15)
AML with mutated chromatin, RNA-splicing genes, or both†	275 (18)	**RUNX1** (39), **MLL**^{PTD} (25), **SRSF2** (22), *DNMT3A* (20), **ASXL1** (17), **STAG2** (16), *NRAS* (16), *TET2* (15), *FLT3*^{ITD} (15)
AML with *TP53* mutations, chromosomal aneuploidy, or both‡	199 (13)	**Complex karyotype** (68), **–5/5q** (47), **–7/7q** (44), ***TP53*** (44), **–17/17p** (31), **–12/12p** (17), +8/8q (16)
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB–MYH11*	81 (5)	**inv(16)** (100), *NRAS* (53), +8/8q (16), +22 (16), *KIT* (15), *FLT3*^{TKD} (15)
AML with biallelic *CEBPA* mutations	66 (4)	***CEBPA***^{biallelic} (100), *NRAS* (30), *WT1* (21), *GATA2* (20)
AML with t(15;17)(q22;q12); *PML–RARA*	60 (4)	**t(15;17)** (100), *FLT3*^{ITD} (35), *WT1* (17)
AML with t(8;21)(q22;q22); *RUNX1–RUNX1T1*	60 (4)	**t(8;21)** (100), *KIT* (38), –Y (33), –9q (18)
AML with *MLL* fusion genes; t(x;11)(x;q23)§	44 (3)	**t(x;11q23)** (100), *NRAS* (23)
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *GATA2, MECOM(EVI1)*	20 (1)	**inv(3)** (100), –7 (85), *KRAS* (30), *NRAS* (30), *PTPN11* (30), *ETV6* (15), *PHF6* (15), *SF3B1* (15)
AML with *IDH2*^{R172} mutations and no other class-defining lesions	18 (1)	***IDH2***^{R172} (100), *DNMT3A* (67), +8/8q (17)
AML with t(6;9)(p23;q34); *DEK–NUP214*	15 (1)	**t(6;9)** (100), *FLT3*^{ITD} (80), *KRAS* (20)
AML with driver mutations but no detected class-defining lesions	166 (11)	*FLT3*^{ITD} (39), *DNMT3A* (16)
AML with no detected driver mutations	62 (4)	
AML meeting criteria for ≥2 genomic subgroups	56 (4)	

Papaemmanuil et al. NEJM 2016

Driver Mutations With Effect on OS

Table 2. Driver Mutations with the Strongest Effect on Overall Survival and Other Clas

Variable	Frequency in Study Cohort (N = 1540)	Hazard Ratio for Death (95% CI)	P Value
	no. of patients (%)		
Main effects			
inv(3), *GATA2, MECOM(EVI1)*	23 (1)	2.9 (1.8–4.7)	9×10^{-6}
TP53	98 (6)	1.7 (1.4–2.2)	7×10^{-8}
Complex karyotype	159 (10)	1.4 (1.2–1.7)	2×10^{-5}
BRAF	9 (1)	1.4 (1.1–1.8)	0.009
SRSF2	89 (6)	1.4 (1.1–1.7)	0.003
$FLT3^{ITD}$	341 (22)	1.4 (1.2–1.7)	0.0008
+21	39 (3)	1.3 (1.1–1.6)	0.001
−5/5q	107 (7)	1.3 (1.1–1.5)	0.0007
−17/17p	74 (5)	1.3 (1.1–1.5)	0.003
+13	21 (1)	1.3 (1.1–1.5)	0.004
−7	88 (6)	1.3 (1.1–1.5)	0.003
−9q†	53 (3)	1.2 (1.1–1.5)	0.01
+22†	26 (2)	1.2 (1.1–1.4)	0.008
NPM1	436 (28)	0.7 (0.6–0.9)	0.0004
*CEBPA*biallelic	73 (5)	0.6 (0.4–0.7)	4×10^{-5}
t(15;17), *PML–RARA*	65 (4)	0.3 (0.2–0.4)	5×10^{-8}
inv(16), *CBFB–MYH11*	82 (5)	0.3 (0.2–0.4)	4×10^{-9}
Gene–gene interactions			
NPM1–$FLT3^{ITD}$–DNMT3A	93 (6)	1.5 (1.2–1.9)	0.0002
MLL^{PTD}–$FLT3^{TKD}$	10 (1)	1.4 (1.2–1.8)	0.0005
DNMT3A–$IDH2^{R140}$	47 (3)	1.4 (1.1–1.8)	0.007
STAG2–$IDH2^{R140}$	11 (1)	0.8 (0.6–0.9)	0.01
NPM1–$FLT3^{TKD}$	53 (3)	0.7 (0.6–0.9)	0.009
DNMT3A–RAD21	19 (1)	0.7 (0.5–0.9)	0.0008
Other class-defining lesions			
t(v;11), not *MLLT3–MLL*	37 (2)	1.4 (1.0–2.1)	0.06
ASXL1	70 (5)	1.3 (1.0–1.6)	0.04
ZRSR2	13 (1)	1.3 (1.0–1.7)	0.04
RUNX1	133 (9)	1.1 (0.9–1.3)	0.5
t(9;11), *MLLT3–MLL*	18 (1)	0.8 (0.4–1.4)	0.5
$IDH2^{R172}$	39 (3)	0.8 (0.6–1.0)	0.07
t(8;21), *RUNX1–RUNX1T1*	63 (4)	0.7 (0.4–1.0)	0.03

Papaemmanuil et al. NEJM 2016

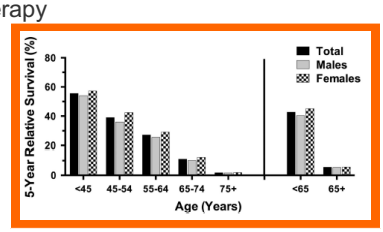
Myeloid Molecular Panel- UNC

Gene	Prognostic	Therapeutic
ASXL1	Poor-risk	-
BCOR	?	-
CEBPA	Favorable	-
DNMT3A	Most studies suggest adverse-risk	-
ETV6/TEL	?	-
EZH2	?	-
FLT3-ITD/TKD	Yes (ITD)	Yes
IDH1	?	Yes- in dev.
IDH2	?	Yes
KIT	Yes in CBF AML	Yes- in dev.

Gene	Prognostic	Therapeutic
NPM1	Favorable	-
NRAS	?	-
RUNX1	Poor-risk	-
SF3B1	?	-
SRSF2	Poor-risk (though not in ELN)	-
STAG2	?	-
TET2	?	-
TP53	Poor-risk	-
U2AF1	?	-
WT1	?	-
ZRSR2	Poor-risk (though not in ELN)	-

AML Outcomes

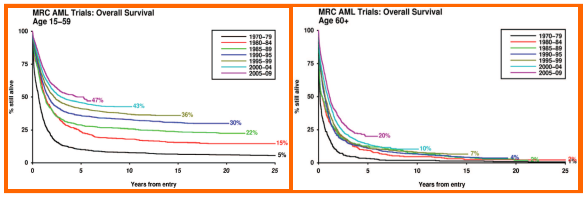
- Extremely poor prognosis with conventional therapy



- 5-year survival rates = 40% in <65 yrs and <10% in ≥65 yrs

Walter, Leukemia 2015

AML Outcomes Over Time



- Improvements in survival likely due to supportive care and allogeneic transplantation
- No new drugs approved in AML since 1990…UNTIL 2017!

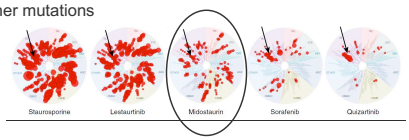
Burnett AK, Hematology Am Soc Hematol Educ Program 2012

Management of AML in 2018

- Divided into therapy for younger (<60-65 years) versus older pts (>65 yrs)
- Induction chemotherapy-> Goal = CR (<5% blasts)
- "Standard" induction = "7+3"
  - 7 days of continuous infusion cytarabine
  - 3 days of anthracycline (daunorubicin v. idarubicin)
- Induction therapy advanced with new drug approvals for specific subsets of AML pts
  - **Midostaurin-** FLT3 inhibitor; front-line treatment with 7+3 for newly dx AML with FLT3 mutations
  - **CPX-351**- Liposomal Cytarabine and Daunorubicin approved for t-AML and AML with MDS-related changes or preexisting MDS
  - **Gemtuzumab**- Anti-CD33 antibody with calicheamicin toxin- approved in combination with 7+3
  - **Enasidenib-** IDH2 inhibitor, single-agent for relapsed/refractory AML

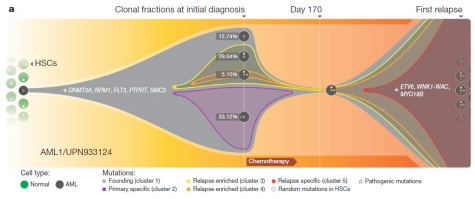
FLT3 as a Target

- FLT3 = fms-like tyrosine kinase-3
  - FLT3 = tyrosine kinase receptor-> cell survival, signaling, and proliferation
- FLT3 mutations seen in 25-30%
  - ITD mutation- most common- 3 to >200 base pairs inserted into FLT3 gene-> constitutive activation of FLT3
    - Younger pts, highly proliferative, most commonly normal cytogenetics, high rate of relapse
  - TKD mutations- less common, neutral prognosis
- Thought to be a secondary "driver" of AML and co-occurs with other mutations



Leik & Levis, Curr Hematol Malig Rep 2017; Levis, Blood 2017; Davis MI Nat Biotechnol 2011

Clonality of AML

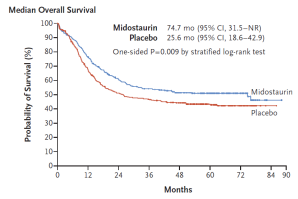


- AML is polyclonal at Dx
- After chemo and/or relapse-> becomes oligoclonal based on dominant clone

Ding et al. Nature 2012

7+3 + Midostaurin

- RATIFY Trial- RP3 trial of 7+3 + Midostaurin 50 mg PO Bid on days 8-21 vs. Placebo in <60 years with FLT3 mut.
- If CR-> Midostaurin added to consolidation and maintenance
- N=717 pts- CR rates = 59% vs. 54% (p=0.15)



- Midostaurin FDA-Approved in combo with 7+3 for newly Dx AML with FLT3 mutation- April, 2017
- First targeted agent approved for AML

Stone RM, et al. NEJM 2016

CPX-351

- Liposomal formulation of 7+3
- RP2 study in newly Dx AML ≥60 yrs vs. 7+3
  - CR rates = 67% vs. 51%, p=0.07
  - Median OS = 14.7 months vs. 12.9 months, lower 60-day mortality with CPX-351
  - Secondary AML appeared to have most benefit
- RP3 study of CPX-351 vs. 7+3 in newly Dx secondary AML 60-75 years
  - N = 309 pts randomized
  - CR rates = 47.7% vs. 33.3% (p=0.016), Median OS = 9.6 months vs. 5.9 months (p=0.005)
- CPX-351 approved for first-line Tx of AML with MDS-related changes and t-AML (August, 2017)
- New SOC for an extremely high-risk AML patient population

Lancet J, ASCO Abstract 2016

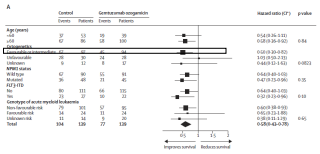
AML with MDS-Related Changes

Cytogenetic abnormalities
Complex karyotype (3 or more abnormalities)
Unbalanced abnormalities
−7/del(7q)
del(5q)/t(5q)
i(17q)/t(17p)
−13/del(13q)
del(11q)
del(12p)/t(12p)
idic(X)(q13)
Balanced abnormalities
t(11;16)(q23.3;p13.3)
t(3;21)(q26.2;q22.1)
t(1;3)(p36.3;q21.2)
t(2;11)(p21;q23.3)
t(5;12)(q32;p13.2)
t(5;7)(q32;q11.2)
t(5;17)(q32;p13.2)
t(5;10)(q32;q21.2)
t(3;5)(q25.3;q35.1)

Arber D, Blood 2016

Gemtuzumab (GO)

- Initially FDA-approved in 2000 for relapsed/refractory AML
  - Taken off market in 2010 due to toxicity & efficacy concerns in 2010
- ALFA-0701- RP3 study of 7+3 + GO vs. 7+3 in newly dx AML 50-70 yrs
  - GO incorporated into consolidation therapy
  - CR rates = 81% vs. 75% with GO (p=0.25), OS and EFS advantage with GO



Castaigne, Lancet 2012

GO- Back to the Future

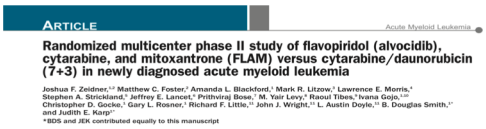
- Re-approved in 2017- in combination with 7+3
- Favorable/Intermediate-risk cytogenetics benefit from GO
- Adverse-risk pts do not benefit
- SOC for Favorable/Intermediate-risk AML
- Consolidation studied only included 2 cycles- is this superior to 4 cycles of HiDAC?
- Unclear benefit over 7+3 with high dose daunorubicin
  - Daunorubicin 60 mg/m^2 studied with GO

How to Manage AML in Younger Pts in 2018

- Clinical trials are still imperative for newly dx AML
- Treatment individualized based on prognostic factors at Dx
- If FLT3 mutation (typically back in 2-4 days)-> 7+3 + Midostaurin
- If favorable/intermediate-risk cytogenetics w/o FLT3 mutation and 50-70 years-> 7+3 + GO
  - If <50 years-> 7+3 with high dose daunorubicin versus 7+3 + GO
- If t-AML, AML with MRC or preexisting MDS-> CPX-351
- Adverse-risk AML- no SOC, **clinical trials** versus 7+3 versus cladribine + 7+3
- Suspect treatment algorithms will continue to evolve as more targeted and selective agents are utilized

Alvocidib

- Novel agent in development for AML
- Potent CDK9 inhibitor
- Studied in >400 AML pts- newly dx & relapsed/refractory



ARTICLE — Acute Myeloid Leukemia

Randomized multicenter phase II study of flavopiridol (alvocidib), cytarabine, and mitoxantrone (FLAM) versus cytarabine/daunorubicin (7+3) in newly diagnosed acute myeloid leukemia

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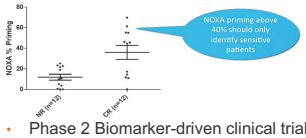
*BDS and JER contributed equally to this manuscript

- CR rates significantly higher with FLAM vs. 1 or 2 cycles of 7+3 (70% vs. 46% vs. 57%, respectively)
- OS no different between either arms
- Predictive biomarkers of response with Alvocidib?

Zeidner J et al, Haematologica 2015

Predictive Biomarkers of Alvocidib

- Alvocidib inhibits MCL-1
  - MCL-1- anti-apoptotic peptide regulated by CDK9 and RNA polym II
- Retrospective BH3 profiling from diagnostic bone marrow samples from FLAM vs. 7+3



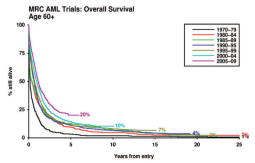
- High NOXA priming score associated with MCL-1 dependence

- Phase 2 Biomarker-driven clinical trial of FLAM in newly dx and relapsed/refractory AML with NOXA priming ≥40%
- Phase 1 study of Alvocidib followed by 7+3 in newly dx AML

Zeidner JF & Karp JE. Leuk Res 2015; Smith BD, ASCO Abstract 2016

Elderly AML

- Age >60-65 years
- Dismal prognosis- 5-year survival <10%
  - Increased toxicity and mortality with intensive induction
  - Higher rates of adverse-risk features
  - More aggressive disease biology independent of risk status
- Have not made significant therapeutic advances



Burnett AK, Hematology Am Soc Hematol Educ Program 2012

Management of Elderly AML

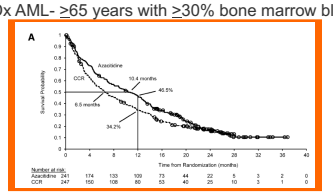
- Optimal management is key area of research
- No “standard of care”
- 1) Decide if patient is fit or unfit for intensive chemo
  - Variety of objective comorbidity scores can be used
  - Many times = subjective assessment
- 2) Obtain diagnostic/prognostic information
  - Adverse-risk dz do poorly with intensive chemo
- 3) Clinical trials imperative for elderly AML

Elderly AML- Fit Patients

- Intensive chemo can be given to select FIT pts up to 75-80 yrs
  - Favorable-risk respond best
- CPX-351- SOC for newly diagnosed secondary AML
  - Pts should be fit to receive intensive chemo- RP3 trial- pts 60-75 yrs
  - Cytopenias tend to be longer with CPX-351
- 7+3- reasonable option for favorable-risk elderly AML
  - Should not use high dose daunorubicin
  - If ≤70 years and not adverse-risk-> add GO to induction
  - Clofarabine- inferior to 7+3 for elderly AML (RP3 trial)
- Hypomethylating agents- Azacitidine or Decitabine
  - Lower intensity, no need for hospitalization, less toxicity
  - Lower rates of CR but unclear if difference in overall outcomes?
- Gemtuzumab- single agent
- Low dose cytarabine

RP3 Study of Azacitidine vs. Physician Choice in AML

- Newly Dx AML- ≥65 years with ≥30% bone marrow blasts

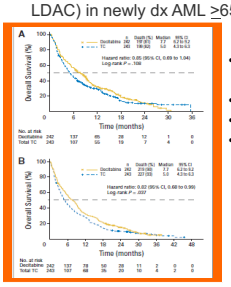


- When compared with pts preselected for intensive chemo (7+3)-> N= 87 randomized
  - Median OS = 13.3 months vs. 12.2 months with Aza vs. 7+3
  - CR rates = 28% vs. 47.7% with Aza vs. 7+3
- Reasonable first-line option in AML- trials in combination

Dombret et al., Blood 2015

Decitabine

- RP3 Study of Decitabine (5 day) vs. Physician choice (BSC or LDAC) in newly dx AML ≥65 years



- Median OS = 7.7 months vs. 5.0 months; p=0.108
- Not FDA-approved
- CR rate = 18%
- Decitabine 10-day regimen: CR rates as high as 50%
  - No randomized trials
  - Potential activity in *TP53* mut

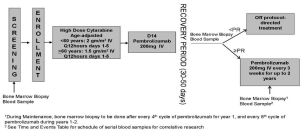
Kantarjian et al. J Clin Oncol 2012; Blum et al. PNAS 2010; Welch J et al. NEJM 2016

Clinical Trials in Elderly AML

- Venetoclax- BCL-2 inhibitor- RP3 trials ongoing in combination with 1) LDAC, 2) Azacitidine
- Pevonedistat- NEDD-8-Activating Enzyme Inhibitor- RP3 trial ongoing in combination with Azacitidine
- Phase 2 study of Azacitidine + Pembrolizumab
  - Multi-institutional trial- Hopkins, UNC, MUSC
  - 2 cohorts- A) Newly Dx AML ≥65 years, B) Relapsed/refractory
  - Enrolling at UNC-> correlative studies to determine predictors of response
- Azacitidine + novel agent strategy

Relapsed/Refractory AML

- Majority of pts who achieve CR-> relapse
- No SOC, outcomes are extremely poor
- Treatment includes intensive salvage chemotherapy versus lower intensity treatments
- Phase 2 Study of High Dose Cytarabine + Pembrolizumab
  - Multi-institutional trial- UNC = Lead site



*During Maintenance, bone marrow biopsy to be done after every 4th cycle of pembrolizumab for year 1, and every 6th cycle of pembrolizumab during years 1-2.
†See Time and Events Table for schedule of serial blood samples for correlative research

- Enrolled 22 pts to date- overall CR rates = 35%
- Correlative studies- predictive biomarkers of response

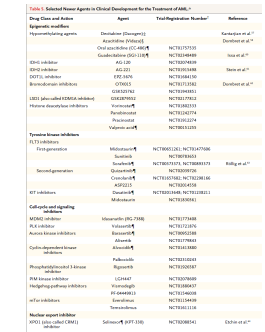
Targeted Therapy

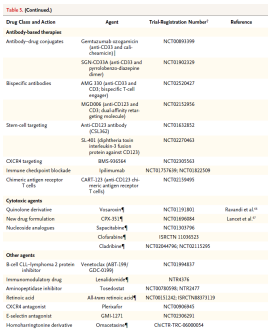
- IDH2 mutations seen in 8-10% of AML
  - $IDH2^{R140}$ and $IDH2^{R172}$ mutations
  - Commonly associated with other mutations
- Enasidenib- First-in-class IDH2 inhibitor- oral agent
- Phase I/II study of Enasidenib in relapsed/refractory AML with IDH2 mutations
  - N=239 pts
  - Safe and effective dose = 100 mg daily
  - Overall response rate = 39%, CR rates = ~20%
  - Median duration of response = 5.6 months
- Enasidenib well tolerated- differentiation syndrome can occur in 12% of pts- need to be rigorously monitored
- FDA-approved for Tx of relapsed/refractory AML with IDH2 mutation in August, 2017

Where Do We Go From Here?

- Multitude of new agents being explored in AML
- Beginning to understand how best to Tx small subsets of pts
- Predictive biomarker strategies promising- moving away from 1-size fits all Tx
- Immunotherapeutic strategies represent promising avenue of exploration in AML

Drug Development in AML





Dohner, NEJM 2015

Case

- 67 yo M with past medical history significant for Stage I Squamous Cell Carcinoma of Oropharynx in 2015, s/p Cisplatin + XRT, with no evidence of recurrence, presents with progressive fatigue, chest tightness and found to have pancytopenia with WBC = $1.3x10^9$/L, Hb = 7.8 g/dL, and platelet count = $69x10^9$/L. A bone marrow biopsy is performed revealing 20% blasts by manual aspirate differential with multilineage dysplasia. Cytogenetics reveal a highly complex karyotype and NGS mutational testing reveals TP53 mutation. The patient otherwise has an ECOG PS = 0 and is healthy with minimal other comorbidities.

Question 1

What is the next step in the management of this patient?

A) Refer directly for allogeneic stem cell transplant
B) 7+3 induction chemotherapy
C) CPX-351
D) Azacitidine
E) 7+3 + Midostaurin

Conclusions

- AML is a challenging Dz to treat
  - Heterogeneous with diverse genetic subsets
- AML pts have a poor prognosis
- 4 new agents approved in AML in 2017
  - Significantly improving outcomes for subsets of pts
  - Standard Rx's are still unsatisfactory
- Prompt referral to highly specialized cancer centers is warranted
- Clinical trials are imperative in all facets of Dz

Questions?

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