UNC CANCER NETWORK

CANCER TREATMENT IN NORTH CAROLINA **RESEARCH TO PRACTICE**

Live Lecture

February 26, 2020

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OUR PRESENTER

Joshua Zeidner, MD

Dr. Joshua Zeidner is an Assistant Professor of Medicine at University of North Carolina, Lineberger Comprehensive Cancer Center. Dr. Zeidner's expertise is in the management of patients with acute myeloid leukemia, myelodysplastic syndrome and myeloproliferative neoplasms.

His research focuses on drug development, and the design and conduct of innovative clinical trials for patients with acute myeloid leukemia and myelodysplastic syndrome.

Since arriving to University of North Carolina in 2014, Dr. Zeidner has led the expansion and growth of the clinical trials program in the Leukemia group. He currently leads the Leukemia Clinical Trials Research Group where a multitude of cutting-edge clinical trials are available for acute and chronic leukemias, myelodysplastic syndrome and myeloproliferative neoplasms.

His specific clinical research focus encompasses drug development in two distinct pathways in acute myeloid leukemia: 1) cyclin-dependent kinase inhibitors, and 2) innovative immunotherapeutic strategies.

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Acute myeloid leukemia (AML) starts in the . . . .

Bone Marrow	**A**
Brain	**B**
Heart	**C**
Lungs	**D**

Answers to this poll are anonymous

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DISCLOSURES

This activity has been planned and implemented under the sole supervision of the course directors, in association with the UNC Office of Continuing Professional Development (UNC CPD). William A Wood, MD, MPH, and CPD staff have no relevant financial relationships with commercial interests as defined by the ACCME.

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Management of Acute Myeloid Leukemia in 2020: A Paradigm Shift for Older Adults?

Joshua Zeidner, MD
Assistant Professor of Medicine
Leader, Leukemia Clinical Trials Group
University of North Carolina
Lineberger Comprehensive Cancer Center
Twitter: @LeukDocJZ

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Disclosures

- Honoraria: AbbVie, Agios, Celgene, Daiichi Sankyo, Genentech, Pfizer, Tolero
- Consultancy: AsystBio Laboratories, Celgene, Takeda
- Research support: Celgene, Merck, Takeda, Tolero

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Objectives

- To discuss pathogenesis/etiology of AML
- To discuss diagnostic testing in AML
- To discuss management of AML in older patient populations in the context of recent drug approvals
- To highlight investigational agents in development and evolving treatment paradigms for older adults

Case

- 75 yo M with PMHx of chronic myelomonocytic leukemia (CMML) & HTN presented to urgent care in 10/2017 with lower extremity edema and fatigue.
  - CMML diagnosed in December, 2016- WBC = 40,000 with monocytosis, no significant cytopenias, Bone marrow biopsy at Dx revealed 1% blasts, trilineage dysplasia (CMML-0)
- At presentation, WBC = $174x10^9$/L, Diff = range of differentiation, blasts >20%, Hb = 9.6 g/dL, Platelets = $70x10^9$/L, uric acid = 12.0 mg/dL, creatinine = 1.3 mg/dL, LDH = 1,659
- Denies any symptoms of chest pain or dyspnea.
- Bone marrow biopsy = Hypercellular (80%) marrow with 31% blasts + promonocytes consistent with AML
  - Normal cytogenetics (46,XY) and NGS Mutational Panel WNL

Question 1

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

A) 7+3 induction since this patient has AML and AML shall be treated with 7+3
B) IVF's, Leukapharesis
C) IVF's, hydroxyurea cytoreduction, allopurinol
D) IVF's, hydroxyurea cytoreduction, allopurinol, Rasburicase

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Question 2

What is the optimal treatment strategy for this patient?

A) 7+3 induction chemotherapy since this patient has AML and AML shall be treated with 7+3
B) CPX-351 Induction Chemotherapy
C) Azacitidine
D) Azacitidine + Venetoclax
E) Clinical Trial

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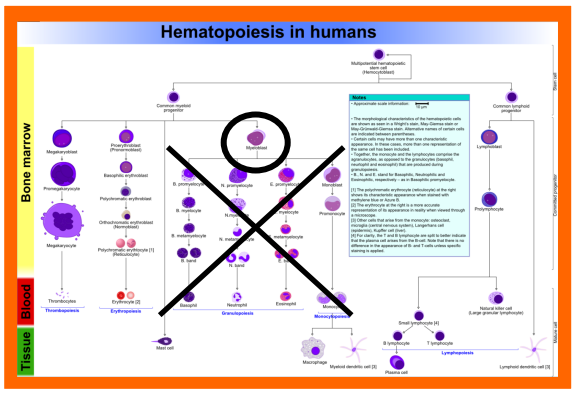
What is AML?



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

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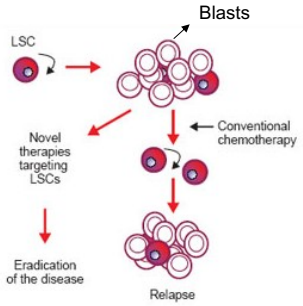
Pathogenesis of AML

- 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



UNC LINEBERGER Cancer Control 2004- H. Lee Moffitt Cancer Center and Research Institute UNC CANCER CARE

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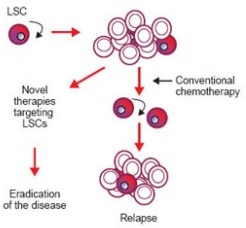
How To Cure AML?

- 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

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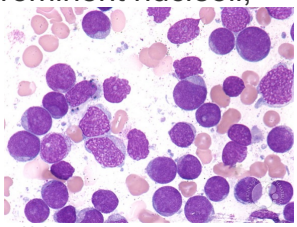
Pathology of AML

- 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

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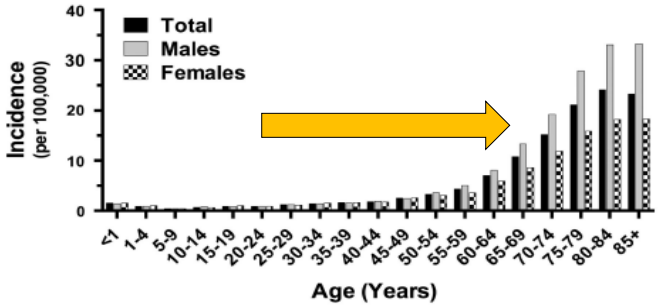
Epidemiology of AML



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

SEER Data, Walter, Leukemia 2015

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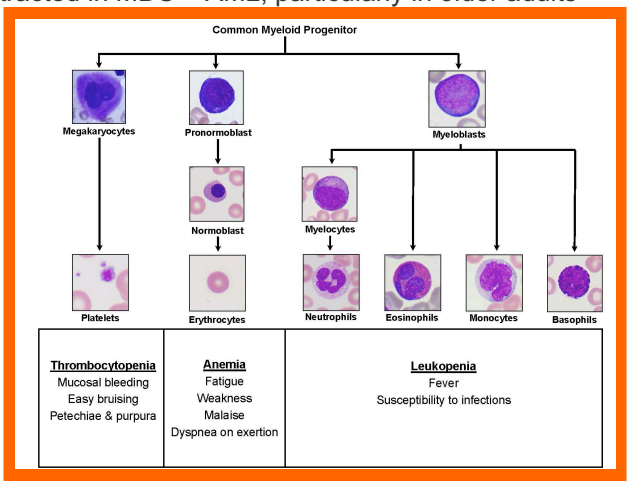
Clinical Presentation

- Rapid onset of symptoms over 1-2 weeks, can be more protracted in MDS-> AML, particularly in older adults



Duncan D et al., Acute Leukemia Textbook 2017.

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Classification/Prognostication

- FAB Classification outdated (M0-M7)
- Genetic information critical for prognostication
- European LeukemiaNet Classification 2017

ELN Risk	Cytogenetic/Molecular	Incidence-Younger pts	Incidence-Older pts
Favorable	• t(8;21); inv(16); t(16;16) • NPM1 mutation w/o FLT3-ITD mut. OR with FLT3-ITD^{low} • Biallelic mutated CEPBA	41%	20%
Intermediate	• Mutated NPM1 and FLT3-ITD^{high} • Wild-type NPM1 w/o FLT3-ITD or with FLT3-ITD^{low} • t(9;11) • Other	37%	49%
Adverse	• Inv(3); t(3;3); t(6;9); t(v;11); -5; del(5q); -7; -17/abnl(17p); complex • Wild type NPM1 & FLT3-ITD^{high} • Mutated RUNX1, ASXL1, TP53	22%	31%

Mrozek, J Clin Oncol 2012; Dohner, Blood 2017

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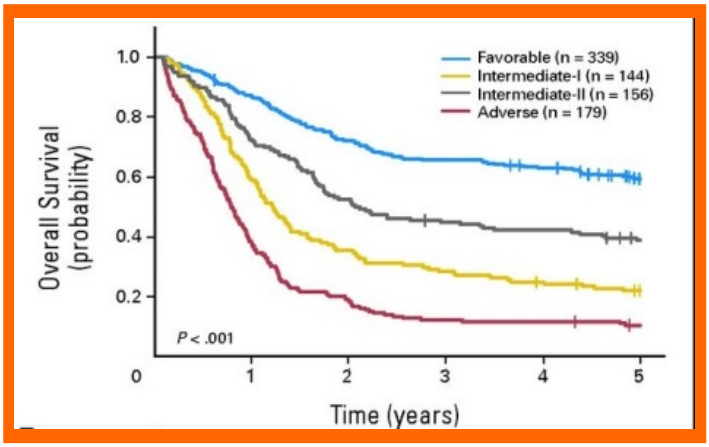
Do Risk Groups Matter?

- Risk groups validated to predict outcome



Mrozek, J Clin Oncol 2012

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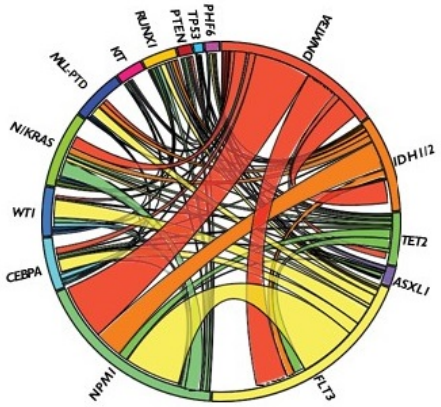
AML is a Heterogeneous Disease



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	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

Patel, NEJM 2012

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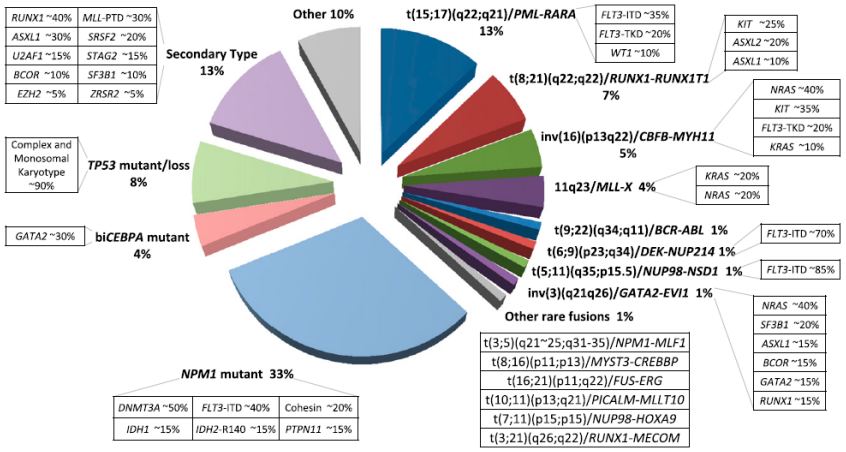
Complexity of Molecular Mutations in AML



Grimwade, Blood 2016

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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

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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^{-6}
Complex karyotype	159 (10)	1.4 (1.2–1.7)	2×10^{-6}
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(x;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

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Myeloid Molecular Panel- UNC

- NGS Panel of 33 genes- most commonly mutated in MDS/AML
- Performed on all diagnostic bone marrow aspirates in MDS/AML
- Recheck at time of relapse- evolving area
- Mutations can be prognostic, therapeutic, and/or can monitor minimal residual disease (MRD)

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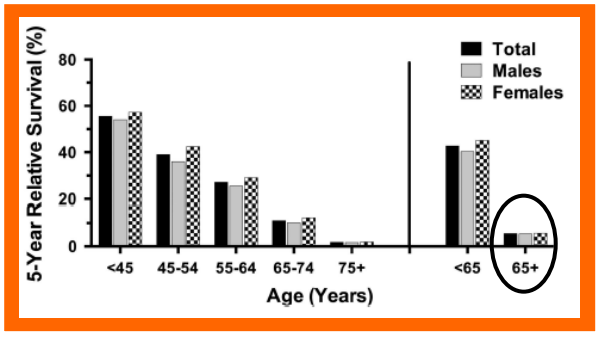
AML Outcomes

- Extremely poor prognosis with conventional therapy



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

Walter, Leukemia 2015

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Question 3

Have overall outcomes improved in AML patients over time?

A) No, long-term survival has not changed over time

B) Yes, long-term survival has improved steadily since 1970's in both younger & older pts but this is not due to chemotherapy

C) Yes, long-term survival has improved since 1970's in younger pts due in large part to supportive care and transplant but much less so in older pts

D) Yes, long-term survival has improved steadily since 1970's in both younger & older pts due to more effective chemotherapy

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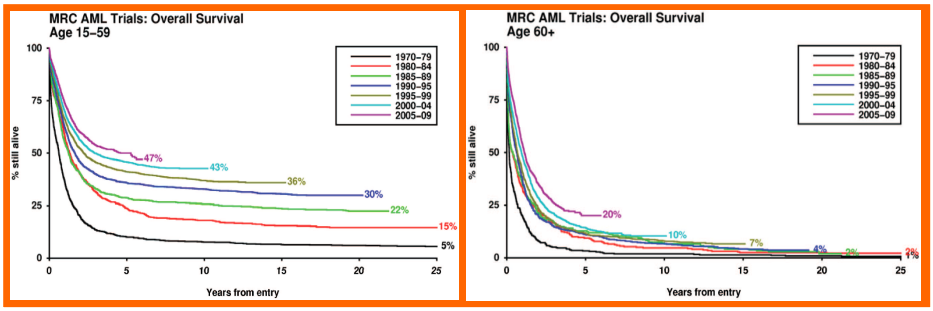
AML Outcomes Over Time



- 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

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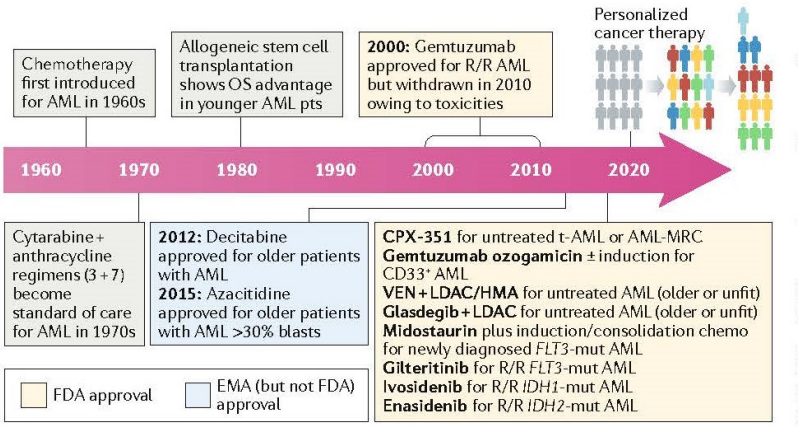
Treatment Landscape of AML since 1960



Dinardo, Nat Rev Clin Oncol 2019

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Question 4

Why do elderly (>60-65 years) AML patients have worse outcomes than younger patients?

A) Older patients are more frail and less apt to tolerate intensive therapies
B) Higher proportion of adverse-risk
C) Higher proportion of secondary AML
D) Treatment nihilism in the community
E) All of the above

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Why Do Elderly AML Have Poor Prognosis?

- Age- tend to be more frail, more comorbidities
  - Less able to tolerate intensive therapy
  - Allogeneic transplant mainly performed in ≤70-75 years
- Biology of disease
  - Increased risk of adverse-risk karyotype & mutations- TP53
- Increased incidence of secondary AML from MDS
  - Very poor prognosis
- Lack of effective Tx options, treatment nihilism?

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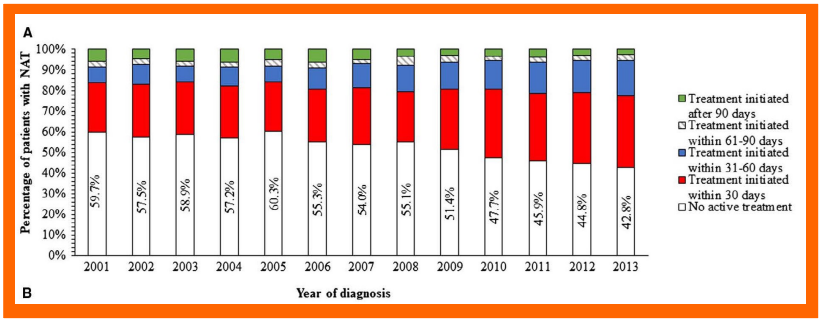
Many Elderly AML Pts Not Treated in Community



- Retrospective analysis from SEER database- 2001-2013
- 14,089 AML pts diagnosed b/w 66-99 years
- Overall trend of more pts being treated with chemotherapy agents over time- still significant proportion untreated

UNC LINEBERGER Zeidan, Cancer 2019 UNC CANCER CARE

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Intensive Chemo in Elderly

- Elderly AML defined as age >60-65 years
- Intensive chemo- SOC for <60 years
- Older adults have significantly higher rates of toxicity and lower clinical efficacy with 7+3 induction

Table 5. Mortality within 30 days of initiation of induction

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y
No. patients	364	242	270	79
Early deaths* by performance status, no./no. total patients (%)				
0	3/129 (2)	8/72 (11)	9/73 (12)	2/14 (14)
1	6/180 (3)	6/112 (5)	20/126 (16)	7/40 (18)
2	1/46 (2)	6/34 (18)	16/52 (31)	7/14 (50)
3	0/9 (0)	7/24 (29)	9/19 (47)	9/11 (82)

Table 6. Treatment outcomes

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y
No. patients	368	246	274	80
Response, no. (%)				
CR	235 (64)	113 (46)	109 (39)	26 (33)
Resistant disease	99 (27)	91 (37)	101 (37)	29 (36)
Median overall survival, no. (95% CI)	18.8 (14.9-22.6)	9.0 (8.1-10.2)	6.9 (5.4-7.7)	3.5 (1.4-6.1)
No. patients with CR	235	113	109	26
Median disease-free survival, no. (95% CI)	21.6 (15.8-25.5)	7.4 (6.5-8.8)	9.3 (6.3-10.2)	8.9 (5.6-10.8)

- Even those with good ECOG PS have poor outcomes w/ 7+3 in elderly
- Can be done in select scenarios in >65 years (i.e. favorable-risk dz)

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Appelbaum, Blood 2006

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CPX-351- Liposomal "7+3"

- Liposomal formulation of 7+3- designed to mitigate toxicity of 7+3 and improve efficacy- **true intensive chemo**
- Clinical activity noted in a randomized phase 2 study in newly Dx AML ≥60 years- CPX-351 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
- Data led to a randomized phase 3 study of CPX-351 vs. 7+3 in newly Dx AML with MDS-Related Changes, t-AML, or Secondary AML from MDS/CMML in pts 60-75 years
  - Older adults fit for intensive chemotherapy
  - Primary endpoint = OS

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Lancet, Blood 2014; Lancet, J Clin Oncol 2018

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AML with MDS-Related Changes

- Presence of preexisting MDS OR:
- Morphology- multilineage dysplasia (≥50% dysplasia in ≥2 lineages)
  - W/O NPM1 or biallelic CEBPA mutations
- Presence of MDS-related cytogenetics
  - Complex Karyotype
  - -7/del(7q)
  - Del(5q)/t(5q)
  - i(17q)/t(17p)
  - -13/del(13q)
  - Del(11q)
  - Del(12p)/t(12p)
  - Idic(X)(q13)
  - t(11;16)
  - t(3;21)
  - t(1;3)
  - t(2;11)
  - t(5;12)
  - t(5;7)
  - t(5;17)
  - t(5;10)
  - t(3;5)

Arber, Blood 2016

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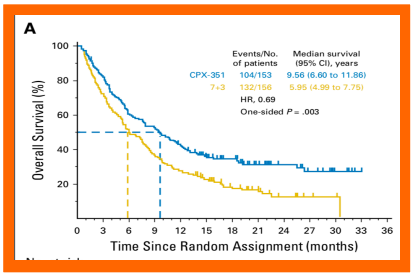
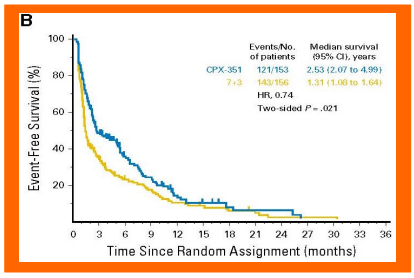
CPX-351 > 7+3 in Older Adults with AML with MRC





- CPX-351 led to superior outcomes vs. 7+3 in older, fit adults with AML with MRC
- Median OS 9.6 vs. 6 months, p = 0.003
- CR rates = 48% vs. 33%, p=0.016, similar CR duration
- CPX-351 led to superior outcomes post-BMT

Lancet, Blood 2014; Lancet, J Clin Oncol 2018

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CPX-351 Summary

- CPX-351 FDA-approved for management of AML with MRC, treatment-related AML or AML from preexisting MDS/CMML
  - No age restriction by label but studies have only conferred benefit in older adults **up to age 75 years**
  - Studies ongoing in other patient subpopulations- i.e. younger AML pts, other risk groups, combination strategies
- This study highlights that 7+3 may not be a useful comparator
  - Dismal outcomes with 7+3 and should not be used in this older adverse-risk pt population
- CPX-351 new SOC for older, **FIT** AML pts with AML with MRC- best done in pts who may be BMT candidates
  - Subsets of pts who truly benefit evolving area
- Moves the needle slightly- still need better therapies

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Low-Intensity Strategies

- Multiple studies have shown that any Tx leads to improved OS compared with best supportive care alone
- Low dose cytarabine (LDAC)- old standard- improved OS compared with best supportive care- CR rates with LDAC = 18% and median OS 6-7 months[1]
- Hypomethylating agents- Azacitidine or Decitabine- not approved for AML but generally reimbursable
  - Approved for MDS
  - Has been used as SOC in USA for >10 years
- Combination therapies now leading to superior outcomes

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1) Burnett, Cancer 2007

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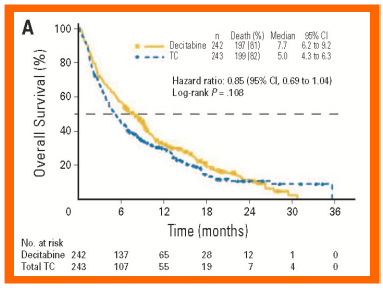
Decitabine

- Randomized Phase 3 study of Decitabine (5 days) vs. Physician choice (LDAC or Best Supportive Care) for newly Dx elderly (≥65 years) AML



- N=485 pts; Median age = 73 yrs
- Intermediate & Poor-risk cytogenetics
- CR rates = 17.8% vs. 7.8%
- Median OS = 7.7 months vs. 5.0 months- p= 0.106
- Not FDA-approved

Kantarjian, J Clin Oncol 2012

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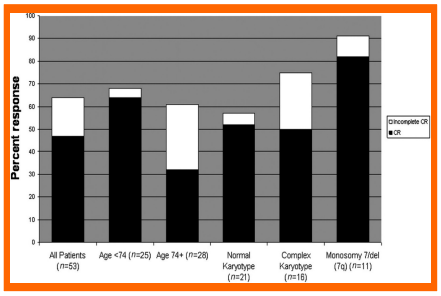
Decitabine- 10 days

- Phase II Study of newly dx AML ≥60 years not candidates for intensive chemo[1]



- N=53 pts, median age = 74 yrs
- CR/CRi rate = 64%
- Median OS ~1 year
- Subsequent studies have suggested high CR's in TP53 mut AML[2]

- Enthusiasm for 10-day tempered after randomized phase 2 study showed no improvement versus 5-days[3]

1) Blum, PNAS 2010; 2) Welch, N Engl J Med 2016; 3) Short, Lancet Haematol 2019

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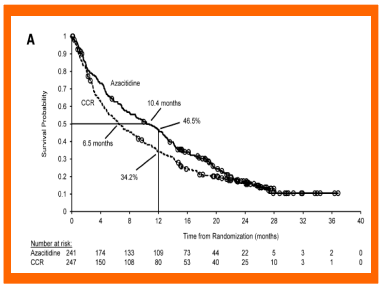
Azacitidine

- Randomized Phase 3 study of Azacitidine vs. Physician Choice (7+3, LDAC, Best Supportive Care) in newly Dx AML ≥65 years with ≥30% blasts



- N=488 pts; Median age = 75 yrs
- Intermediate & Poor-risk cytogenetics
- CR rates = 27.8% vs. 25.1%
  - 7+3 = 47.7%
- Median OS = 10.4 months vs. 6.5 months, p= 0.10 but reached significance censoring for subsequent Tx

- Pts preselected for 7+3-> N=87 randomized
- Median OS = 13.3 months vs. 12.2 months
- Despite lower CR rates, should 7+3 be used at all in elderly?

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Dombret, Blood 2015

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Summary of HMA's

- Reasonable first-line strategy in all older AML pts (≥65 years)
  - Particularly in pts who are not BMT candidates
- No data comparing HMA's to CPX-351 but no advantage to 7+3 over Azacitidine in ≥65 years
- HMA's are less toxic than intensive chemo, outpatient
- Disadvantages- Tx continues indefinitely, low CR rates- can take a few months to see response, cytopenias can persist
- How can we improve HMA's?

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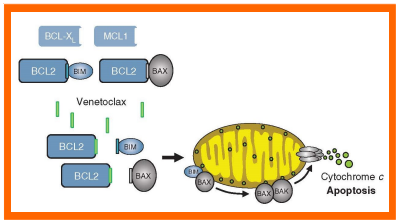
HMA's + Venetoclax

- Venetoclax- oral BCL-2 inhibitor- modest response rates as single agent in R/R AML- 20%



- Phase 1b study of HMA + Venetoclax in newly dx AML ≥65 years
- Eligibility = ineligible for intensive chemo due to:
  - Age >75 years
  - Cardiac Dz
  - Prior anthracyclines
  - High prob. Of mortality

- Arm A: Decitabine 20 mg/m^2 IV x 5 days + Venetoclax
- Arm B: Azacitidine 75 mg/m^2 IV x 5 days + Venetoclax
- Safe dose chosen- 400 mg daily

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Dinardo, Blood 2019

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HMA's + Venetoclax

- Median age = 74 years
- Most had de novo AML (75%)
- CR/CRi rates = 67%, median duration of CR = 11.3 months
- Similar CR rates b/w Azacitidine and Decitabine
- Median OS = 17.5 months

Subgroup	Evaluable for response/OS, n (%)	CR + CRi, n (%)	n for Median duration of CR + CRi	Median duration of CR + CRi, mo (95%CI)	Median OS, mo (95%CI)
All patients	145	97 (67)	97	11.3 (8.9, NR)	17.5 (12.3-NR)
Cytogenetic risk					
Intermediate	74 (51)	55 (74)	55	12.9 (11, NR)	NR (17.5-NR)
Poor	71 (49)	42 (60)	42	6.7 (4.1, 9.4)	9.6 (7.2-12.4)
Age					
≥75 y	62 (43)	40 (65)	40	9.2 (6.4, 12.5)	11 (9.3-NR)
<75 y	83 (57)	57 (69)	57	12.9 (9.2, NR)	17.7 (14.2-NR)
AML					
De novo	109 (75)	73 (67)	73	9.4 (7.2, 11.7)	12.5 (10.3-24.4)
Secondary	36 (25)	24 (67)	24	NR (12.5, NR)	NR (14.6-NR)
Mutations*					
FLT3†	18 (12)	13 (72)	13	11 (6.5, NR)	NR (8-NR)
IDH1 or 2‡	35 (24)	25 (71)	25	NR (6.8, NR)	24.4 (12.3-NR)
NPM1	23 (16)	21 (91)	21	NR (6.8, NR)	NR (11-NR)
TP53	36 (25)	17 (47)	17	5.6 (1.2, 9.4)	7.2 (3.7-NR)

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Dinardo, Blood 2019

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Venetoclax Summary

- Based on promising data from phase 1b-> Venetoclax given accelerated FDA-approval for Tx of newly Dx AML + HMA's
  - >75 years or comorbidities that preclude intensive chemo
- New SOC for elderly AML?
- How do we define fitness for intensive chemo vs. low-intensity strategies?
- 2 ongoing Randomized Phase 3 Trials- Aza + Venetoclax vs. Aza & LDAC + Venetoclax vs. LDAC
  - Primary endpoint = OS
- Unanswered questions- challenging to give in community
  - Myelosuppression frequent- how to dose in cytopenias?
  - Drug interactions with CYP3A4 inhibitors
  - Dose ramp-up over 3-5 days

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Tx Options Post-Venetoclax?

- Despite encouraging response rates-> almost all pts who respond will ultimately relapse
- Median OS = 2.4 months in pts with relapsed/refractory Dz after Aza/Ven[1]
- In pts with FLT3, IDH1 or IDH2 mutations, targeted Tx options available- majority do not have a targeted Tx option
- MCL-1- BCL-2 family member- anti-apoptotic peptide up-regulated in AML
- MCL-1 appears to be a dominant mechanism of resistance after Ven-> targeting MCL-1 rational Tx approach[2-3]
- **UNC lead site on a randomized phase 2 study of Alvocidib (CDK9 inhibitor-> MCL-1 inhibition) +/- low dose cytarabine (LDAC) in pts with relapsed/refractory AML after Venetoclax 1st line Tx**

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1) Maiti, Blood[ASH Abstract] 2019; 2) Konopleva, Cancer Disc 2016; 3) Ramsey, Cancer Disc 2018

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Other Low-Intensity Tx for Newly Dx Elderly AML

- Glasdegib- Hedgehog inhibitor + LDAC
  - Randomized phase 2 study- Glasdegib + LDAC vs. LDAC[1]
  - Median OS = 8.8 months vs. 4.9 months
  - LDAC not useful comparator, not commonly used
- LDAC + Venetoclax
  - Phase 1b study- CR/CRi = 54%, Median OS = 10.1 months[2]
  - Option for prior HMA-treated secondary AML
  - Randomized phase 3 study ongoing
- Ivosidenib- IDH1 inhibitor
  - N=34 pts, CR+CRh = 42%, Median OS = 12.6 months[3]
  - How does this compare to HMA + Ven or HMA?
  - Option in prior HMA-treated pts with IDH1 mut

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1) Cortes, Leukemia 2018; 2) Wei, J Clin Oncol 2019; 3) Roboz, Blood 2019

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Paradigm Shift?

- Treatment nihilism has existed for elderly AML pts in community
- Multitude of available agents- overall outcomes remain poor
- Low-intensity Tx evolving- shifting to younger pts, combination therapies to improve outcomes
- Biomarker-based approaches critical- which pts predicted to respond versus resistance?
- Genomic sequencing (NGS) critical to inform Tx decisions- future strategies will likely be based on full sequencing panels

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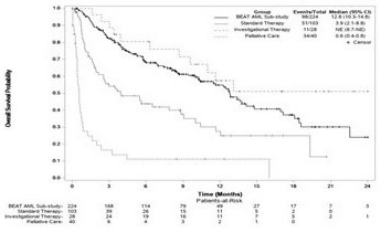
Clinical Trials

- **Despite Tx advances-> clinical trials should be 1st option**
  - Improve clinical outcomes- outcomes remain poor and CR not durable
  - Understand which pts benefit from specific Tx
  - Mitigate toxicity and improve QOL
- Beat AML- Multi-institutional precision-medicine based trial
  - >60 years, all pts receive genomic profiling w/in 1 week
  - Multiple Tx arms w/ investigational agents based on genomic profile
  - Enrolling pts at UNC



Burd, Blood [ASH Abstract] 2019

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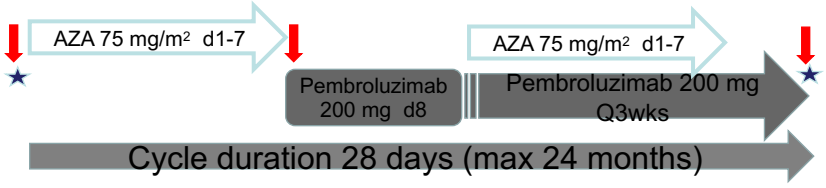
Clinical Trials- Azacitidine + Pembrolizumab

- Phase 2 Study of Azacitidine + Pembrolizumab in 1) Relapsed/Refractory AML, 2) Newly Dx AML ≥65 years



- Collaboration with Johns Hopkins (Lead PI: Ivana Gojo)
- Newly Dx AML- CR/CRi = 53% in evaluable pts
- Well tolerated but immune-related AE's can occur
- Immunogenomic biomarkers of response ongoing
- Combination strategies

Gojo, Blood[ASH abstract], 2019

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Back to Case

- After cytoreduction and management of TLS-> enrolled on Phase 2 Study of Azacitidine + Pembrolizumab
- Achieved CR after 2 cycles of Tx and has been in CR since 11/2017
- No hospitalizations after 1st being hospitalized at Dx
- Completed 2 years of therapy and now on Aza maintenance
  - Pembro-induced hypothyroidism
- Normal QOL and no limitations- currently 77 years old

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Conclusions

- AML is a challenging Dz to treat
  - Heterogeneous with diverse genetic subsets inform Tx decisions
- Elderly AML pts now have many Tx options
  - Should be referred to specialized centers
  - Targeted Tx approaches will continue to move field forward and lead to improved patient outcomes
- Venetoclax-based Tx-> Paradigm shift in management of elderly AML?
  - Can we predict who will respond best? Who will be resistant?
  - What to do after Venetoclax?
- Clinical trials are imperative in all facets of Dz

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Questions?

E-Mail: Joshua_Zeidner@med.unc.edu
Office: 919-962-5164
Twitter: LeukDocJZ

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UNC Cancer Network Telehealth Team

Tim Poe, *Director*
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Veneranda Obure, *A/V Support Engineer*
Jon Powell, PhD, *Continuing Education Specialist*

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UPCOMING LIVE LECTURES

CANCER TREATMENT IN NORTH CAROLINA **PATIENT CENTERED CARE**

Live Lecture

March 11
12:00 PM

Meeting the Needs of Undocumented Patients with Cancer
Julia Rodriguez-O'Donnell, LCSW, OSW-C

CANCER TREATMENT IN NORTH CAROLINA **RESEARCH TO PRACTICE**

Live Lecture

March 25
12:00 PM

Cancer Immunotherapy Toxicities Identification and Management in North Carolina: Updates for 2020
Frances Collichio, MD

For a complete listing and details on coming events visit:
www.unccn.org/events

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SELF-PACED, ONLINE COURSES

RN and Allied Health

Self-Paced, Online Course

Nutrition and the Aging Brain in Cancer Care

Melissa Walter, MPH, RDN, LDN

Medical and Surgical Oncology

Self-Paced, Online Course

New Indications for Radiotherapy

Andrew Wang, MD

Today's lecture will be available in *April 2020* as a ***FREE***, Self-Paced, Online Course

For a complete listing and details on coming events visit:

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SELF-PACED, ONLINE COURSES

CANCER TREATMENT IN NORTH CAROLINA PATIENT CENTERED CARE

Self-Paced, Online Course

The Benefits of Exercise for Cancer Patients

Gabrielle Brennan, MS, ACSM EP-C, CET

Today's lecture will be available in *April 2020* as a ***FREE***, Self-Paced, Online Course

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Understanding
Ovarian Cancer

Victoria Bae-Jump, MD, PhD

February 28
12:00 PM

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