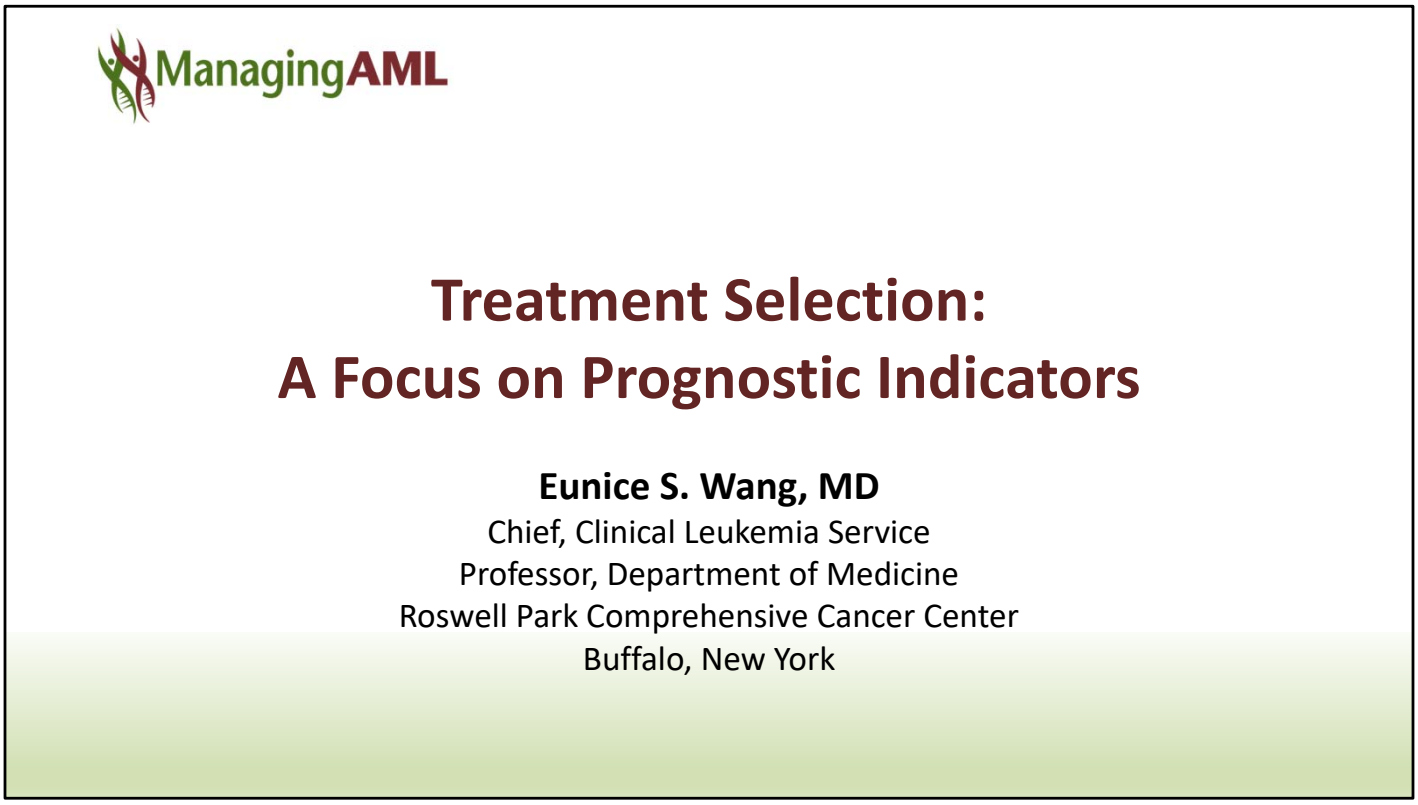


Welcome to *Managing AML*. I am Dr. Eunice Wang, Chief of the Leukemia Service at the Roswell Park Comprehensive Cancer Center in Buffalo, New York. Today, I will be discussing treatment selection focused on prognostic factors. Let's begin now.

Faculty Disclosure

- Dr. Eunice Wang has relevant financial relationships related to advisory activities and consulting from AbbVie Inc., Amgen Inc., Bristol-Myers Squibb Company, Gilead, GlaxoSmithKline plc, Janssen Pharmaceuticals, Inc., Jazz Pharmaceuticals plc, and Kite Pharma, as well as consulting from Astellas Pharma US, Inc., Novartis AG, Pfizer Inc., and PharmaEssentia Corporation. She is on speakers' bureau for AbbVie, Astellas, DAVA Oncology, Kite, Stemline Therapeutics, Inc., Novartis, and Pfizer. Dr. Wang is also on the Data Safety Monitoring Boards of AbbVie, Gilead, and Rafael Pharmaceuticals, Inc.

These are my disclosures.

Learning Objectives

Upon completion of this educational activity, participants should be able to:

- Discuss the limitations of clinical trial criteria used to differentiate patients who are “fit” versus “unfit” for intensive induction therapy
- Assess the role of performance status in determining patient fitness for intensive induction therapy
- Outline factors that increase the likelihood of therapeutic resistance
- Investigate the impact of comorbidity status on outcomes in both high- and low-intensity treatment groups

I'd like to start by outlining the learning objectives for this exercise. First, I'm going to start by discussing the limitations of clinical trial criteria, which are often used to differentiate patients into fit versus unfit categories for intensive induction chemotherapy. In particular, I'd like to discuss the role of performance status and comorbidities in determining patient fitness for intensive induction therapy, as well as mention other factors that can increase the likelihood of therapeutic resistance or treatment failure. Lastly, I'd like to discuss the impact again of the comorbidity status on outcomes and how this can affect or not affect the outcomes of both high dose as well as low dose chemotherapy regimens for AML patients.

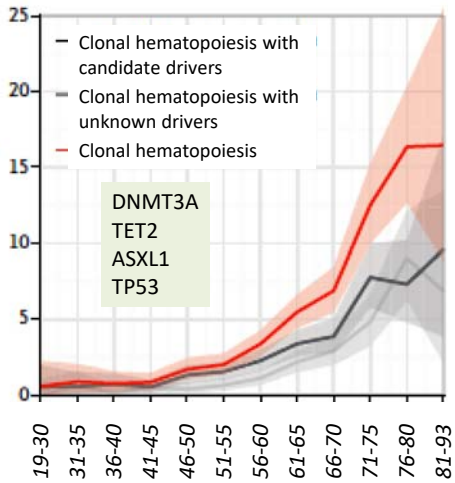
AML is a Disease of Older Individuals

As we all know, for those clinicians who treat AML, AML is a disease of older individuals. Due to clonal hematopoiesis and age-related changes, due to increased mutational burden, we know that patients who present with AML are typically in their late 60s, 70s, and even 80s, with the median age of presentation between 67 to 70 years.

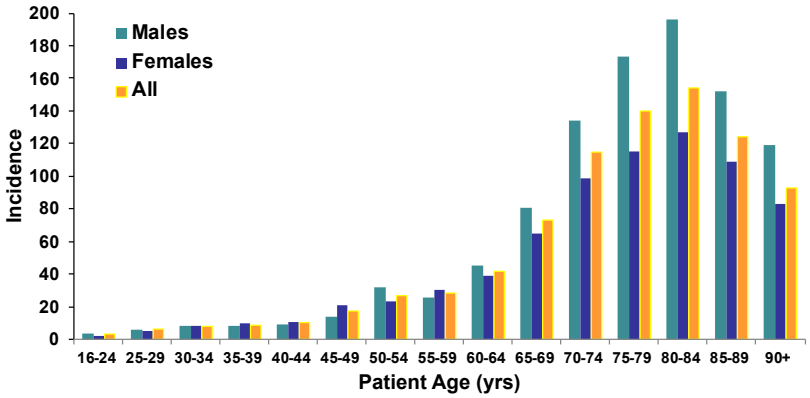
Treatment Selection:
A Focus on Prognostic Indicators

Prevalence of AML in Adults (USA)

Prevalence of CHIP by age



Median age of presentation: 67 to 70 years old



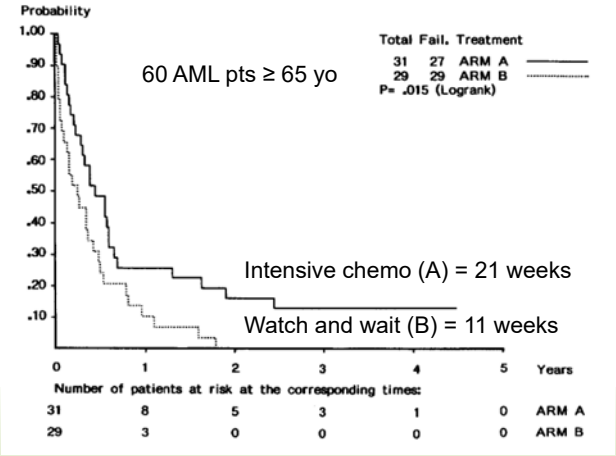
Jaiswal S, et al. *N Engl J Med.* 2014;371:2488-2498.; Juliusson G, et al. *Blood.* 2009;113(18):4179-4187.

As you can see here, the prevalence of AML increases rapidly when we get to the 60, 70, and 80 category. Patients who are considered young in AML terms are those under the age of 60 years of age, whereas the majority of patients are considered older with an age 60 to 65 and above.

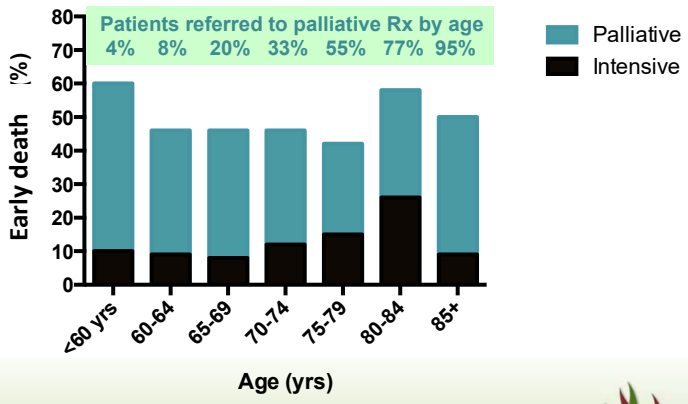
Treatment Selection:
A Focus on Prognostic Indicators

Older Patients Benefit from Intensive Chemotherapy

Randomized phase 3 trial



Swedish AML registry



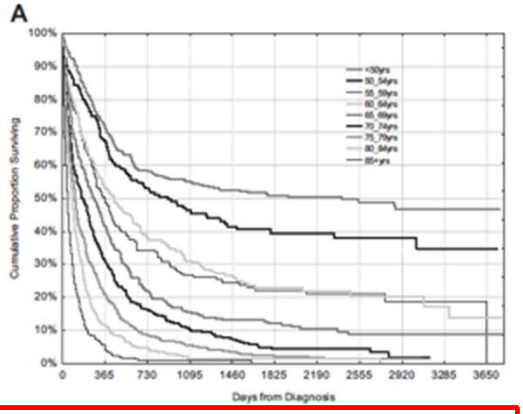
Lowenberg B, et al. *J Clin Oncol.* 1989;7(9):1268-1274.; Juliussen G, et al. *Blood.* 2009;113(18):4179-4187.

Do these older patients, many of whom have other medical problems and are more frail with decreased functional status, do well with intensive chemotherapy? Well, based on data acquired in the 1970s and '80s, we know that even older patients with AML can benefit from treatment as opposed to no treatment.

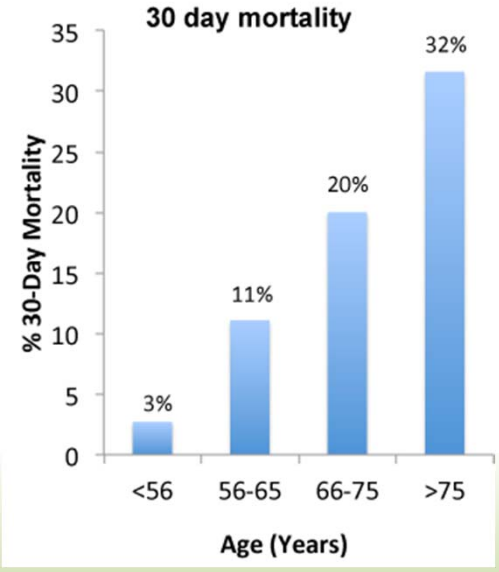
This study shown here on the left-hand side, 60 AML patients greater than or equal to 65 years of age were randomized to receive intensive induction chemotherapy with cytarabine and anthracycline-based regimens versus no treatment or treatment with just transfusion support and hydroxyurea. As you can see, that even in this very limited study of 60 patients, those that got the intensive chemotherapy fared better than those that got supportive care and transfusions only. Data from the Swedish registry in 2009 further confirmed this on a grander scale by looking at all patients who received induction chemotherapy in their country over a period of time. As you can see, many older patients 60, 75, and above, were offered palliative care. Even in these older patients up to the age of 85, those receiving intensive chemotherapy, again, did better with lower rates of early death, defined as death within the first 30 days from their diagnosis.

Treatment Selection:
A Focus on Prognostic Indicators

But…Have Lower Response Rate, Higher Mortality



Intensive chemo	Early death (<30 days)
75-79 years	22%
80-84 years	30%
85+ years	40%

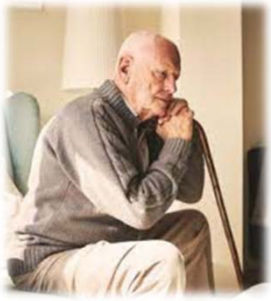


Juliussen G, et al. *Blood.* 2009;113(18):4179-4187.; Applebaum F, et al. *Blood.* 2006;107:3481-3486.

However, we also know that these older patients with less functional abilities who are more frail tend not to do nearly as well with intensive induction chemotherapy as younger patients. Shown here on the left-hand side is data showing that despite the benefit of intensive chemotherapy, the early death rate from treatment-related causes in the elderly patient can be all the way up to 20% to 40%. This mortality rate that we see with treatment-related mortality increases with the age on average of the patients being treated.

Treatment Selection:
A Focus on Prognostic Indicators

Meet Our Patient



Patient Notes

- 71-year-old man presented with acute shortness of breath and fatigue
- WBC 22K (55% myeloblasts), hgb 6 gm/dl, platelets 34K
- PMHx: Prior MI s/p stents, hypertension, localized prostate ca (radiation only)

Physical Exam Findings: ECOG 1

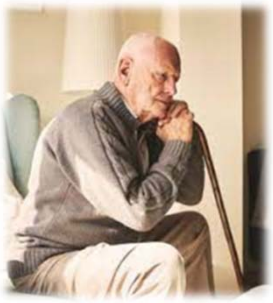
- Easily fatigued man, appears stated age in no acute distress
- Clear lungs bilaterally with no wheezes or rales
- Heart rate tachycardic with regular rate and rhythm

I'd like to discuss now a case presentation, which can illustrate some of the challenges we have and how we clinically make the determination whether an individual patient is considered "eligible" or capable of receiving intensive induction therapy.

This is a 71-year-old gentleman who presents with acute worsening of shortness of breath and worsening fatigue. Evaluation in his emergency room or the urgent care center, demonstrates a white blood cell count of 22,000 with 55% myeloblasts on the peripheral smear. Hemoglobin was markedly decreased at 6 grams per deciliter, and platelets were very low at 34,000. Prior medical history for this individual patient includes a significant cardiac history with prior myocardial infarction, requiring prior intervention with cardiac stent placement. Patient has a long-standing history of hypertension, as well as localized prostate cancer, for which he received radiation. On exam, he is a somewhat older individual who looks fine at rest, but can be easily fatigued with any sort of exertion. He's tachycardic. His lungs are clear,

Treatment Selection:
A Focus on Prognostic Indicators

Meet Our Patient



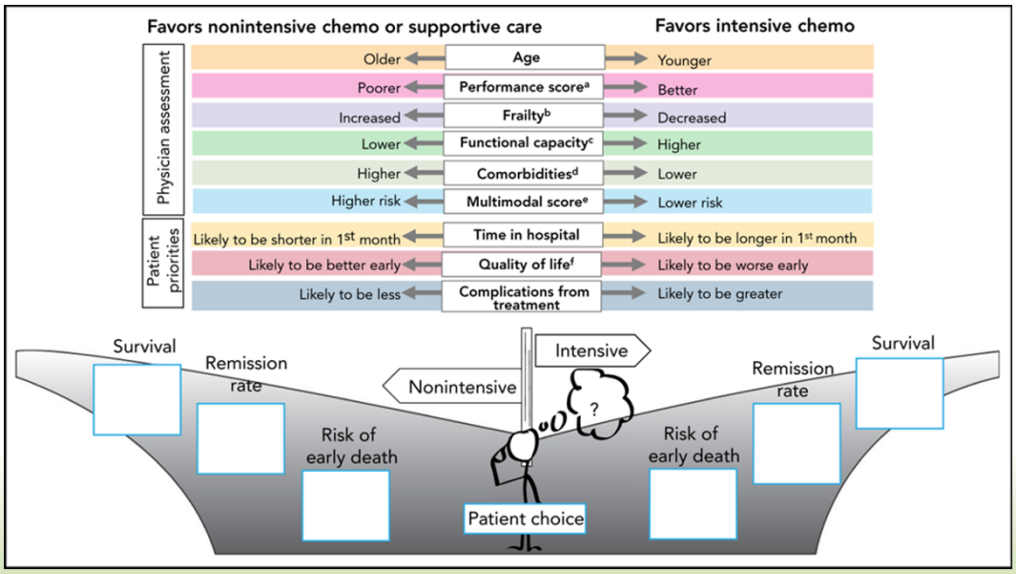
Labs

- Normal renal and liver function
- Marrow shows 82% myeloblasts (MPO+) with Auer rods
- Karyotype: Complex karyotype (≥3 aberrations including del(17p)
- NGS: p53 mutation

and he has normal kidney and liver function on his laboratory values. Bone marrow biopsy, to diagnose the acute myeloid leukemia, confirms 82% myeloblasts with Auer rods. Follow-up studies demonstrated complex karyotype, meaning, greater than or equal to three cytogenetic aberrations, including deletion in 17p chromosome. Mutational profiling demonstrates the presence of a p53 mutation.

Treatment Selection:
A Focus on Prognostic Indicators

Fitness for Intensive Chemotherapy: A Continuing Conundrum



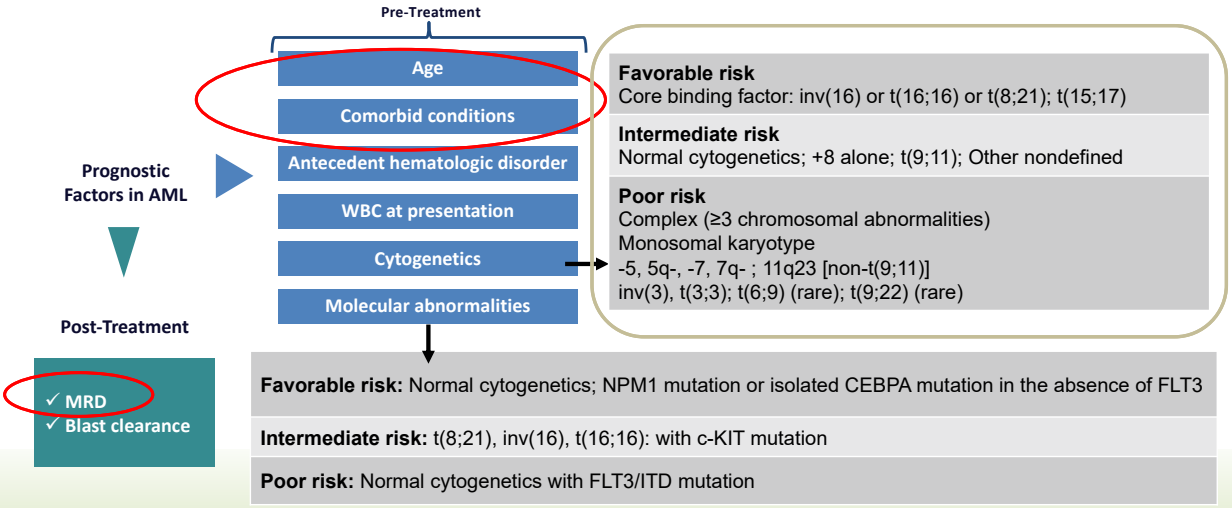
Wei AH. *Blood*. 2021;138(5):356-358.

How would we determine whether this patient is fit or unfit for intensive chemotherapy? Now, there are a number of factors that we look at, both in the patient's presentation, as well as in our chemo regimens, that help us make this determination.

Shown here is a graphic that shows the different factors that can make one lean one way or the other for an individual patient. Obviously, the older the patient, the poorer their performance status, the more frail they look, and their ability to ambulate to certain distance or perform activities of daily living can be important markers of whether a patient can tolerate intensive therapy. We also know that patients who have a significant comorbidity index, or many, many medical problems who spent a lot of time in the chair, in the bed, or in and out of the hospital are also expected to do worse. We need to also consider for these patients, whether they would fare well with an intensive chemotherapy regimen, which is going to require them to be in the hospital for four or five or six weeks as an inpatient, as opposed to their quality of life and their ability to come back and forth to the clinic for an outpatient regimen.

Treatment Selection:
A Focus on Prognostic Indicators

Traditional and New Prognostic Factors in AML



AML=acute myeloid leukemia; CEBPA=CCAAT/enhancer binding protein α; FLT3=FMS-like tyrosine kinase 3; ITD=internal tandem duplications; MRD=minimal residual disease; NPM1=nucleophosmin; WBC=white blood cell

[1]Grimwade D, Hills RK. *Hematology Am Soc Hematol Educ Program.* 2009:385-395; [2]NCCN Clinical Practice Guidelines in Oncology. Acute myeloid leukemia. Version 1. 2016.

Patient priorities need also to be considered in this treatment decision planning because certain individuals will have strong preferences as to which treatment regimen they would prefer based on their personal needs, as well as medical and other factors. The traditional prognostic factors in AML have included high white blood cell count, high tumor burden as reflected by high LDH levels, and conventional cytogenetics. However, increasingly, we are being able to demonstrate that mutational profiling, particularly in patients who have a normal karyotype, can be incredibly important. We also know that newer biomarkers, including methods that we now have available to measure minimal or measurable residual disease at the time of remission can also be a powerful indicator of long-term outcome.

Lastly, we are increasingly aware that consideration not only of the patient's age, but other factors may be equally important in selecting for patients for this regimen. Given the fact that many individuals are all in the same age range, it's important to look at each individual carefully to determine whether this is an 80-year-old that might do well with intensive or a 60-year-old that might not.

How to Define Fit vs Unfit in AML Therapy

Criteria	Fit	Unfit
Age	18-59 years	≥ 60 years with issue or ≥ 75 years
Performance status	ECOG 0-2	ECOG 3-4
Organ function	Normal	Abnormal/decreased
Comorbidities	Low comorbidity index	High comorbidity index
MD opinion	Able to tolerate intensive chemotherapy for any reason	Unable to tolerate intensive chemotherapy for any reason

How have we defined fit and unfit in AML therapy? Well, again, traditionally, we have viewed age as the first cut-off. Meaning, patients between the ages of 18 and 59, in general, are considered fit, and those who are greater than or equal to 60 years old, who have some medical issue or problem may be considered unfit. In general, though, we have been a little bit more aware that 60- to 65-year-old patients can be diverse in their presentation in their functional status. More and more, when we look at patients that are considered unfit, we're using a higher age cutoff now of 75 years and above.

This is perhaps the only cancer that we treat in the modern era, where we have specific treatment regimens only for patients 75 and above. ECOG performance status, or their ability to perform daily tasks can be perhaps the most important of the factors and we'll discuss that a little bit later. Patients who have abnormal organ function, who have underlying liver, kidney, pulmonary, cardiac comorbidities, and high comorbidity indexes are considered general not good candidates for intensive therapy, and there can be other factors as we mentioned, personal preference, social-economic issues, financial considerations, personal preferences, any of those issues, psychiatric considerations, that may make the physician less likely to offer an inpatient based regimen.

Treatment Selection:
A Focus on Prognostic Indicators

Ferrara Criteria for Unfitness for Intensive Chemo

- An age older than 75 years
- Congestive heart failure or documented cardiomyopathy with an EF ≤50%
- Documented pulmonary disease with DLCO ≤65% or FEV1 ≤65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
- On dialysis and age older than 60 years or uncontrolled renal carcinoma
- Liver cirrhosis Child B or C, or documented liver disease with marked elevation of transaminases (>3 times normal values) and an age older than 60 years, or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis
- Active infection resistant to anti-infective therapy
- Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
- ECOG performance status ≥3 not related to leukemia
- Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy

Ferrera F, et al. *Leukemia.* 2013;27:997-999.

In general, we've relied upon these criteria, the Ferrara criteria, which were developed in 2013 and published as potentially a laundry list encompassing many of the factors that I just mentioned and actually defining each of the severities of organ dysfunction, which comprise not a good candidates.

These include congestive heart failure, cardiomyopathy with an EF under 50%, pulmonary function tests with patients who have underlying COPD, cirrhosis, dialysis, active infection, current mental illness, and performance status where they're really not able to take care of themselves and that counts as three and above.

Modified Ferrara Criteria: VIALE-A (Phase 3 Ven/Aza Trial)

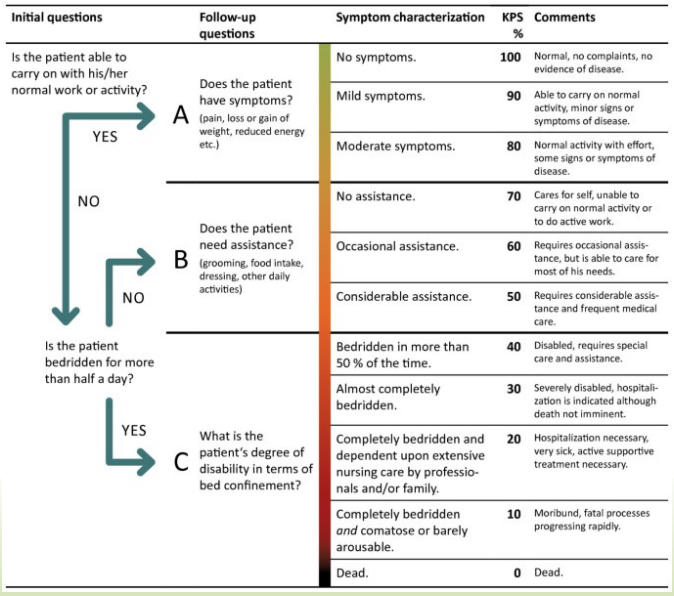
- 75 years of age or older ***OR***
- Any age with at least one of the following conditions
  - History of congestive heart failure requiring treatment or ejection fraction ≤50% or chronic stable angina
  - DLCO ≤65% or FEV1 ≤65%
  - ECOG performance status 2-3 ***OR***
- Considered unfit for intensive chemotherapy per physician discretion
  - Organ dysfunction, active infection, mental illness
  - Disease unlikely to respond given cytogenetic/genomic characteristics

DiNardo CN, et al. *N Engl J Med.* 2020;383(7):617-629.

Now, many of us don't go into that much detail, and we do sometimes feel, for example, that the Ferrara criteria are a little bit too stringent. For example, if I have a patient who has an ejection fraction of 49%, et cetera. Many of us have employed what we call a modified Ferrara criteria, and these were used in the pivotal phase 3 trial VIALE-A to determine those patients who were considered unfit and eligible for enrollment on that trial of venetoclax/azacitidine. In the VIALE-A trial, the modified Ferrara criteria included 75 years of age and above, minimal congestive heart failure, DLCO and ECOG performance status, and physician discretion.

Treatment Selection:
A Focus on Prognostic Indicators

Karnofsky Performance Status (KPS)

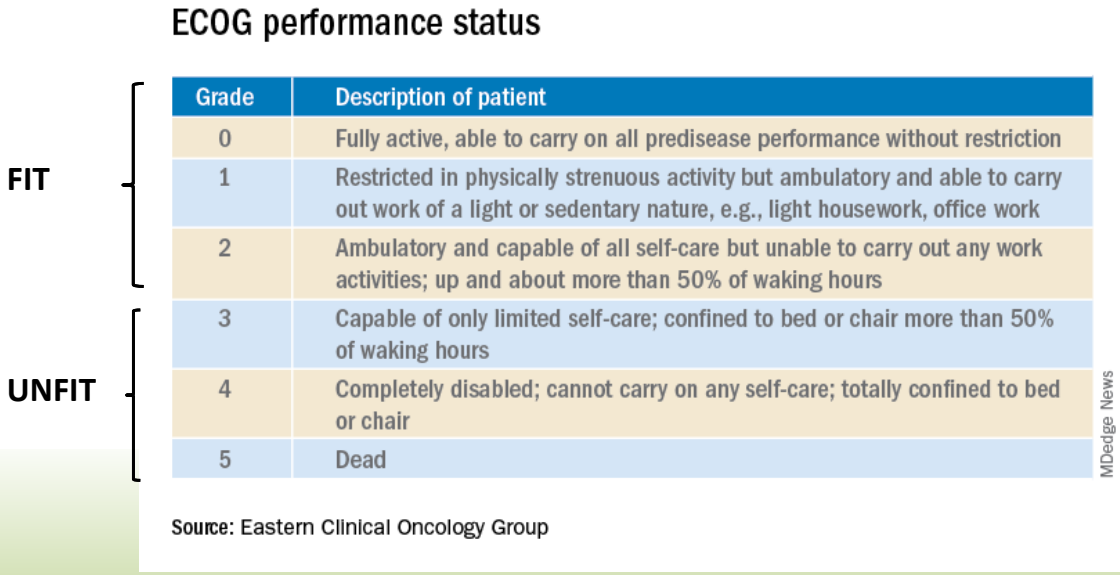


Crooks V, et al. *J Gerontol.* 1991;46:M139-M144.

What are the most commonly used methods to assess performance status? I'm just showing you here the details of each of the most commonly used functional indexes. You can see here that the Karnofsky Performance Status ranks patients from 0% to a 100%. Generally, we'd use a cut off 50% to 90% as fit. Anybody whose Karnofsky Performance Status is under 50% means that they're bedridden for 50% of the time and therefore not eligible for many intensive or even standard of care therapies. Within the fit population, you can see that patients in the 50%, 60% category are requiring a lot of daily assistance with activities as opposed to those who require no assistance or only have mild symptoms which are 90% to 100%.

Treatment Selection:
A Focus on Prognostic Indicators

ECOG (Zubrod/WHO) Performance Status



ECOG performance status

	Grade	Description of patient
FIT	0	Fully active, able to carry on all predisease performance without restriction
	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
	2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
UNFIT	3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
	4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
	5	Dead

Source: Eastern Clinical Oncology Group

The ECOG also known as Zubrod or WHO Performance Status is a little bit more clean-cut. You can see here, this is from zero to five. Anybody three to five is generally considered unfit with patients zero to two generally considered fit enough for intensive chemotherapy, three being the cut-off where there may be some ambiguity, many trials will cut it off at zero to two. Some may consider patients with ECOG two to three.

Treatment Selection:
A Focus on Prognostic Indicators

Charlson Comorbidity Index (CCI)

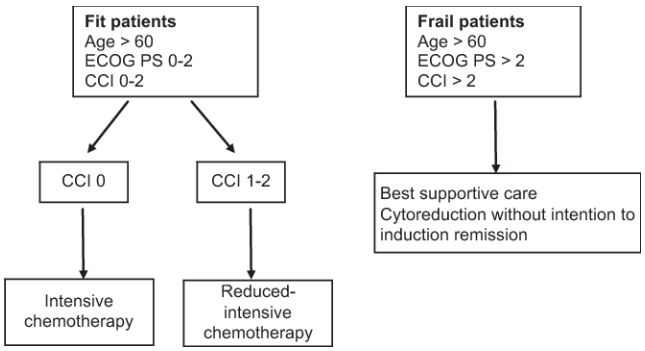
Chronic disease	Weight	Chronic disease	Weight	Chronic disease	Weight
Cerebrovascular disease	1	Myocardial infarction	1	Skin ulcers/cellulitis	2
Congestive heart failure	1	Peripheral Vascular disease	1	Takes warfarin	1
COPD/Asthma	1	Rheumatic disease	1	Leukemia	2
Dementia	1	Ulcer disease	1	Lymphoma	2
Depression	1	Hemiplegia	2	Moderate/severe liver disease	3
Diabetes without end organ	1	Moderate/severe renal disease	2	Metastatic solid tumor	6
Hypertension	1	Diabetes with end organ damage	2	HIV/AIDS	6
Mild liver disease	1	Any tumor	2		

doi:10.1371/journal.pone.0112479.t001

There also are an increasing numbers of other indices and models that have been used to try to predict for outcomes. The Charlson Comorbidity Index, CCI, has been developed by internal medicine specialists for their ability to really delineate out all of the comorbidities that could be affecting patients. The higher the number of these chronic diseases that a patient has, and you can see leukemia is weighted as two, the more likely that these patients are not going to live very long.

Treatment Selection:
A Focus on Prognostic Indicators

Selecting AML Therapy Intensity Based on Clinical Factors



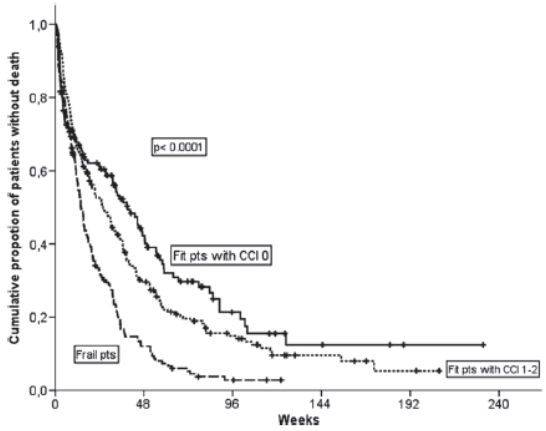


Figure 2. Overall survival of 509 patients with AML according to stratification groups. p was calculated by log-rank test: $p < 0.0001$ for the whole model; $p = 0.09$ when fit patients with Charlson Comorbidity Index (CCI) 0 were compared with fit patients with CCI 1–2.

Do we select AML therapy based on therapy? How good are we at selecting? How good are these factors at predicting for outcomes? In this particular study, we've looked in many times at patients that we consider to be fit and we've looked at how they fare with different performance status outcomes and comorbidity indices. You can see that fit patients who have a comorbidity index of zero can fare quite well, whereas frail patients with high comorbidity indexes and poor performance status have a fairly dismal survival that can be measured in really six months or less.

Treatment Selection:
A Focus on Prognostic Indicators

Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI)

Table 1. Definitions and Weighted Scores of the Pretransplantation Comorbidities Included in the HCT-CI and Their Prevalence Among the Allogeneic Transplantation Patients Admitted to the Intensive Care Unit

Comorbidity	Definitions	HCT-CI Weighted Score	Patients (N = 377) No.	%
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmia	1	16	4
Cardiac	Coronary artery disease, congestive heart failure, myocardial infarction, or EF ≤ 50%	1	55	15
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1	3	1
Diabetes	Requiring treatment with insulin or oral hypoglycemic but not diet alone	1	47	12
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5× ULN, or AST/ALT > ULN to 2.5× ULN	1	56	15
Infection	Requiring continuation of antimicrobial treatment after day 0	1	10	3
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1	4	1
Obesity	Patients with a body mass index > 35 kg/m^2	1	41	11
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1	40	11
Renal, moderate/severe	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2	3	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatic	2	10	3
Peptic ulcer	Requiring treatment	2	11	3
Pulmonary, moderate	DLCO and/or FEV_1 66% to 80% or dyspnea on slight activity	2	123	33
Heart valve disease	Except mitral valve prolapse	3	9	2
Hepatic, moderate/severe	Liver cirrhosis, bilirubin > 1.5× ULN, or AST/ALT > 2.5× ULN	3	16	4
Prior solid tumor	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3	20	5
Pulmonary, severe	DLCO and/or FEV_1 ≤ 65% or dyspnea at rest or requiring oxygen	3	179	47

Abbreviations: CTD, connective tissue disease; DLCO, diffusion capacity of carbon monoxide; EF, ejection fraction; FEV_1, forced expiratory volume in 1 second; HCT-CI, Hematopoietic Cell Transplantation–Specific Comorbidity Index; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; ULN, upper limit of normal.

In the hematologic malignancies, we often consider patients for stem cell transplantation. There is a comorbidity index that has been designed, particularly keeping in mind those patients that might be eligible for subsequent allogeneic stem cell transplantation. You can see here, again very similar criteria just delineating out on these patients with acute leukemia.

Treatment Selection:
A Focus on Prognostic Indicators

Comorbidities and PS on AML Outcome

2792 patients in 2000-2012, national registry, 52.5% (1467) received IC

Table 4. Association between comorbidity, WHO Performance Status and chance of CR in 1467 patients allocated to intensive therapy

	Patients, n (CR%)	*OR, crude estimate (95%CI)*	*OR, adjusted for gender and age (95%CI)*	*OR, adjusted for gender, age and WHO PS/comorbidity (95%CI)*	*OR, adjusted for age, gender, cytogenetics, WBC, prior hematological disease/cancer, and prior cytotoxic treatment and WHO PS/comorbidity (95%CI)*
Comorbidity					
No comorbidity	1106 (74%)	1.0	1.0	1.0	1.0
1 comorbid disease	274 (66%)	0.68 (0.48; 0.96)	0.83 (0.58; 1.19)	0.86 (0.60; 1.24)	1.06 (0.69; 1.63)
⩾2 comorbid disease	87 (63%)	0.61 (0.44; 0.84)	0.73 (0.53; 1.02)	0.76 (0.54; 1.07)	1.02 (0.66; 1.56)
WHO PS (missing, n=21)					
0	488 (79%)	1.0	1.0	1.0	1.0
1	690 (71%)	0.70 (0.53; 0.92)	0.76 (0.96; 0.97)	0.76 (0.57; 1.01)	0.87 0.63; 1.20)
⩾2	289 (60%)	0.39 (0.28; 0.54)	0.43 (0.65; 1.06)	0.43 (0.31; 0.60)	0.49 (0.33; 0.73)

Abbreviations: CR, complete remission; ORs, odds ratios; WBC, white blood cell count; WHO PS indicates World Health Organization Performance Status; 95%CI, 95% confidence interval.

Ostgard LSF, et al. *Leukemia.* 2015;29:548-555.

When you look at comorbidities and performance status, what is potentially more predictive of outcome? Is it the number of conditions that they have or is it their functional state? There are always those patients that come in whose functional state is really being brought on by the disease itself, and that treatment of the disease can improve their functional status and actually make them feel better because their initial presentation is limited by the disease manifestations. However, in general, we feel that functional status and here, the WHO or ECOG is much more clinically relevant and linked to treatment outcome than for example, having one or two comorbidities.

Treatment Selection:
A Focus on Prognostic Indicators

2017 ELN Classification of AML (Based on 7+3)

Risk Status	Cytogenetics	Molecular Abnormalities
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} or Biallelic mutated CEBPA
Intermediate	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse	Mutated *NPM1* and FLT3-ITD^{high} Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions)
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* −5 or del(5q); −7; −17/abn(17p) Complex karyotype,§ monosomal karyotype	Wild-type *NPM1* and FLT3-ITD^{high} Mutated *RUNX1* Mutated *ASXL1* Mutated *TP53*

Döhner H, et al. *Blood.* 2017;129:424-447.

What are other factors that we need to consider when considering a patient for intensive chemotherapy? I think it's important to recognize that even though a patient may be extremely fit and have an excellent performance status with a low comorbidity index and otherwise be a great candidate for intensive chemotherapy, may, despite all of our efforts, have underlying disease, which biologically is unlikely to respond to intensive chemotherapy.

How do we know that? Well, we have through many decades of investigation, determined, even now in the modern era, which cytogenetic abnormalities and which mutational abnormalities predict for poor response to cytarabine and anthracycline-based therapy. Any prognostic classification, and this one, the European LeukemiaNet from 2017 is based on the treatment regimen. You can see here that this is the outcome of patients who are going to do well or not well with standard 7+3.

Treatment Selection:
A Focus on Prognostic Indicators

AML-Composite Model to Estimate Comorbidities in Patients

Comorbidities for AML-CI	HR (95% CI) *P* Value	Assigned Score	
Cardiac	1.6 (1.2-2.3)	1	.05
Diabetes	1.1 (0.9-2.8)	0	.71
Hepatic	1.3 (1.0-1.8)	1	.04
Infection	1.3 (0.9-1.8)	1	.12
Peptic ulcer	1.6 (0.9-2.7)	1	.11
Renal			
Prior malignant neoplasm			
Heart valve disease	1.5 (0.9-2.8)	1	.1
Hyperlipidemia	0.9 (0.7-1.2)	0	.58
Hypertension	1.1 (0.8-1.4)	0	.66
Albumin level, g/dL			
Platelet count, × 103 µL			
LDH level, U/L			
Sex: Male	1.1 (0.8-1.4)	0	.68
Age, y			
0-49	1 [Reference]	0	NA
50-59	1.8 (1.2-2.7)	1	.007
60-69	2.0 (1.3-3.0)	2	.001
≥70	2.5 (1.5-4.0)		<.001
Cytogenetic/molecular risks			
Favorable	1 [Reference]	0	NA
Intermediate	1.8 (1.2-2.8)	1	.009
Adverse	2.8 (1.9-4.3)	2	<.001
Initial regimen intensity			
Low	1.6 (1.1-2.3)	NA	.008
Intermediate	1 [Reference]	NA	NA
High	1.2 (0.9-1.8)	NA	.25

Sorror M, et al. *JAMA Oncol.* 2017;3(12):1675-1682.

There have been models shown here as the AML composite model, which attempts to incorporate both the biological features, as well as some of the functional features and patient-related features into one prediction model. Here, you can see that they take in consideration, not only the comorbidities, they take in consideration certain laboratory values, age, as well as cytogenetic and molecular risk.

Treatment Selection:
A Focus on Prognostic Indicators

Survival Based on ACM and Therapy Intensity in AML Patients

Characteristic	Patients, %		
	Less intensive	Intensive	*P*
Age ≥65 y	87	26	<.0001
Age ≥75 y	43	5	<.0001
Augmented HCT-CI score ≥4	72	52	<.0001
Mean augmented HCT-CI score	5.3	4.2	<.0001
2017 ELN adverse risk group	46	29	<.0001
AML-CM score ≥7	75	46	<.0001
Mean AML-CM score	9.0	6.5	<.0001

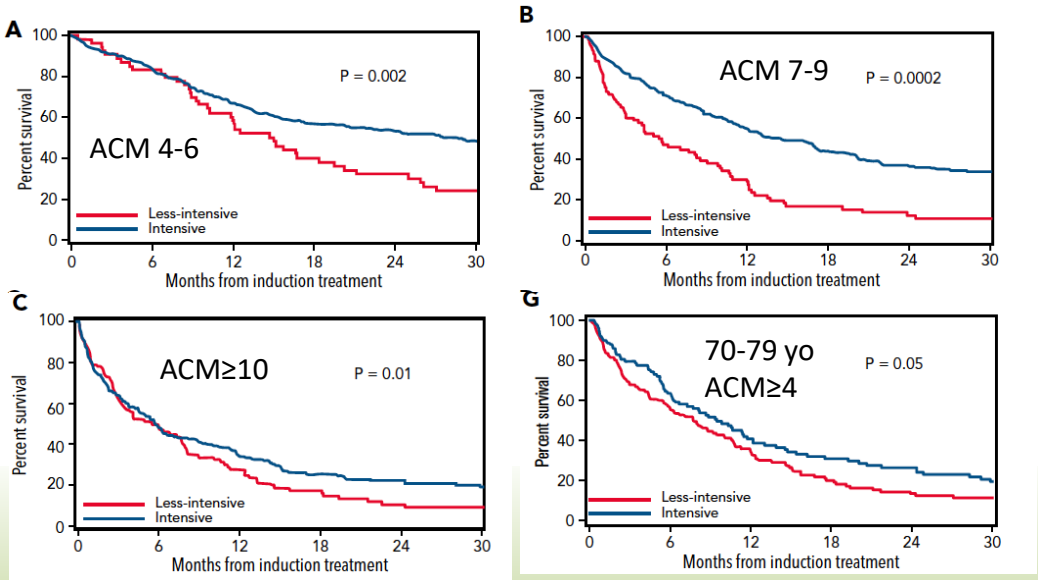
AML-CM cytogenetics combining age, comorbidities, and ELN risk.

Sorror M, et al. *Blood.* 2021;138(5):387-400.

Using this type of integrated model, you can see here that all of the things that we really would predict are really validated. Patients who are younger and are fitter are being offered more intensive therapy, patients who are older are really being offered less intensive therapy. Patients who have high comorbidities, again, lower intensive therapy, patients with cytogenetically or adverse risk category, again, more likely to be offered less intensive therapy, because if you're not going to do well with intensive therapy, why go through the trouble and the risk of exposing the patient to more treatment mortality with an intensive regimen?

Treatment Selection:
A Focus on Prognostic Indicators

Survival Based on ACM and Therapy Intensity in AML Patients



Sorror M, et al. *Blood.* 2021;138(5):387-400.

You can see here that using this integrative model, it's a combination of factors. It's not just one that is going to determine whether a patient does well. A patient could, for example, in that example, I gave before do very well and be very fit enough to tolerate the regimen, but still have refractory disease and short overall outcome because their disease, for example, contains a p53 mutation.

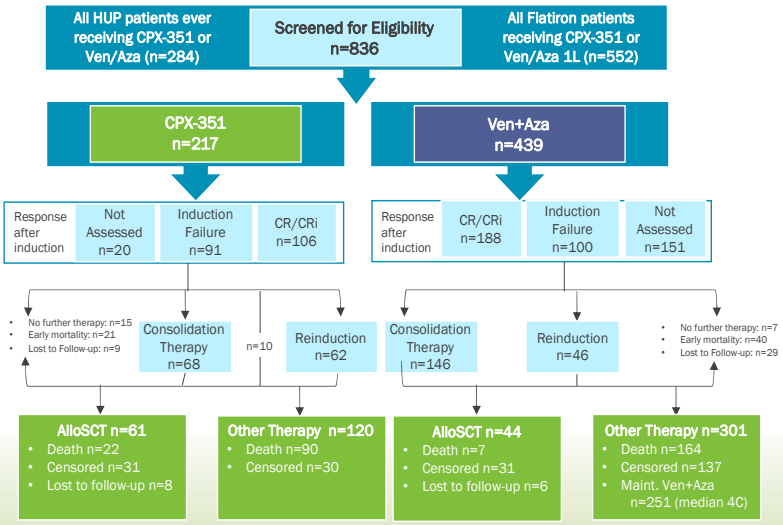
Treatment Selection:
A Focus on Prognostic Indicators

Real-World Outcomes: CPX-351 vs Ven/Aza in ND-AML

Key Eligibility Criteria
- AML (based on BM or PB blasts > 20%)
- Therapy started between 1/1/2017 to 12/31/2020
- 1L with Ven+Aza or CPX-351
- No mixed-phenotype leukemia or APL
- ECOG PS 0-2

2 data sources
1. UPHS (HUP) HER: a 5-hospitals system spanning inpatient and outpatient settings
2. Flatiron Health database: a nationwide compilation of de-identified EHR-derived clinical, biomarker, treatment and mortality data for 2.2 million patients at 800 sites of care

Primary endpoint: OS (time 0 at diagnosis)



Matthews A, et al. ASH 2021.Abstract 795.

How are we using some of these factors in the real world? How do we in the real-world setting select for patients? I'd like to end with just some data presented at the ASH 2021 meeting, where there was a real-world study looking at in the community and academia who gets an intensive chemotherapy regimen with liposomal 7+3, CPX-351, and who gets a lower intensive regimen consisting of venetoclax/azacitidine.

You can see in this retrospective real-world data, there were about 800 patients, both in the community and the academia center who were looked at, who had newly diagnosed AML. About 217 of them had received CPX, 439 had received venetoclax/azacitidine.

Treatment Selection:
A Focus on Prognostic Indicators

Real-World Outcomes: CPX-351 vs Ven/Aza in ND-AML

Patient Characteristics		Ven+Aza (n=439)	CPX-351 (n=217)	*P* value
Median age (range), years		75 (36-88)	67 (21-82)	<0.001
Gender, n (%)	Female	191 (44)	112 (52)	0.056
	Male	248 (56)	105 (48)	
Practice type, n (%)	Academic	149 (34)	103 (47)	<0.001
	Community	290 (66)	114 (53)	
AML type, n (%)	De Novo	226 (51)	63 (29)	<0.001
	Prior MDS/MPN	150 (34)	104 (48)	
	Therapy-related	63 (14)	50 (23)	
ELN risk group, n (%)	Favorable	34 (8)	15 (7)	0.84
	Intermediate	117 (27)	64 (29)	
	Adverse	172 (39)	92 (42)	
	Favorable	34 (8)	15 (7)	

Patient Characteristics		Ven+Aza (n=439)	CPX-351 (n=217)	*P* value
HCT comorbidity index, n (%)	0	116 (26)	69 (32)	0.28
	1-2	156 (36)	69 (32)	
	≥3	82 (19)	35 (16)	
ECOG PS, n (%)	0-1	62 (14)	31 (14)	0.23
	2-4	196 (45)	72 (33)	
High-risk mutations, n (%)	Negative	201 (46)	90 (41)	0.17
	RUNX1	29 (7)	22 (10)	
	ASXL1	42 (10)	14 (6)	
	TP53	57 (13)	33 (15)	

- Patient characteristics demonstrated some imbalance at baseline
- No significant differences in risk groups, comorbidities, PS, or mutational status
- Expected differences in age, practice type, and de novo vs secondary (prior therapy–related AML

Matthews A, et al. ASH 2021.Abstract 795.

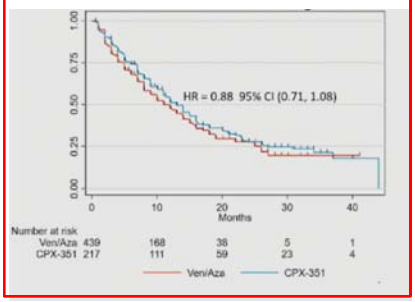
Taking a deeper dive into these two patient populations, you can see that again, there are the same inherent tendencies that I've just discussed that are occurring in real life. You can see that patients receiving venetoclax/azacitidine had a median age of 75 years, as opposed to those who received CPX-351. You can see that patients who had secondary disease were more likely to receive CPX-351. Patients who had prior therapy-related disease also were more likely to get CPX. Patients with de novo disease who might do well without a liposomal cytarabine anthracycline-based regimen were more likely to be offered venetoclax/azacitidine. You can see that this was across the board.

Were there differences in patients being selected for venetoclax/azacitidine versus CPX based on their comorbidity index? The answer was no. How about ECOG performance status? Actually, there was no difference in these patients based on the ECOG performance status. It really was based on age, as well as the type of AML.

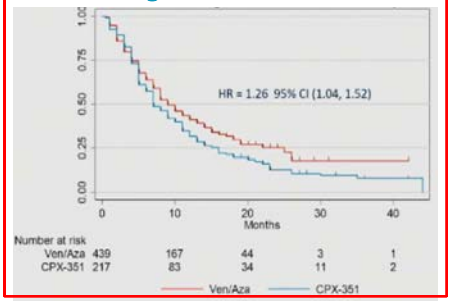
Treatment Selection:
A Focus on Prognostic Indicators

Real-World Outcomes: CPX-351 vs Ven/Aza in ND-AML

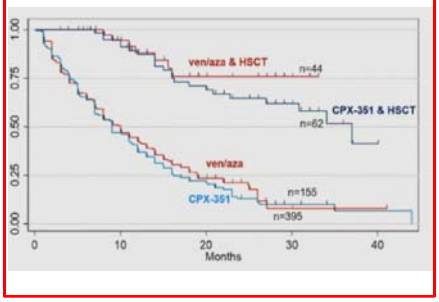
OS From Diagnosis



OS From Diagnosis Censored for HSCT



OS and HSCT



Efficacy

- Ven+Aza and CPX-351 showed similar OS
- HSCT is critical for survival regardless of initial treatment
- Key subgroups did not favor Ven+Aza or CPX-351
- Restricting to CPX-351 pivotal trial inclusion criteria also showed no significant difference in OS
- Across sensitivity analyses, HR for OS did not significantly favor Ven+Aza or CPX-351

Transplant Outcomes	Ven+Aza	CPX-351
n, (%)	44 (10)	61 (28)
Median time to HSCT (range), days	186 (87-578)	171 (34-903)
Median OS with HSCT, months	NR	37
Median OS without HSCT, months	10	9

Matthews A, et al. ASH 2021.Abstract 795.

What were the outcomes of the study? In these two patient populations, older, unfit patients, more newly diagnosed disease, as opposed to younger, fit patients, more secondary, more therapy-related disease, there were equivalent outcomes. You can see on the left-hand side, the overall survival from diagnosis was the same. When you accounted for patients going to transplant, that also was the same. The only difference between patients enrolled retrospectively in this analysis was that patients, regardless of what induction chemotherapy they got, if they were able to go to stem cell transplantation, they did universally better than those that didn't.

Treatment Selection:
A Focus on Prognostic Indicators

Real-World Outcomes: CPX-351 vs Ven/Aza in ND-AML

Flatiron & UPHS	CPX-351 (n=217)	Ven+Aza (n=439)	*P* value
Median cycles (range)	2 (1-5)	4 (1-28)	N/A
30-day mortality, % (95% CI)	5 (2-8)	5 (3-7)	0.51
60-day mortality, % (95% CI)	10 (6-14)	13 (10-16)	0.10
Diagnosis of infection, % (95% CI)	51 (42-61)	20 (15-25)	<0.00005

UPHS Only	CPX-351 (n=52)	Ven+Aza (n=59)	*P* value
Febrile neutropenia, % (95% CI)	90 (82 -98)	54 (42-67)	<0.00005
Culture positive infection, % (95% CI)	67 (55-80)	36 (23-48)	0.0004
Mean inpatient stay, days (95% CI)	41 (37-45)	15 (10-20)	<0.00005

Authors' Conclusions

- OS was similar for Ven+Aza and CPX-351
- CPX 351 and Ven+Aza had similar OS across subgroups and sensitivity analyses
- Ven+Aza and CPX-351 had similar early mortality
- Additional studies are confirming findings and exploring additional endpoints

Safety

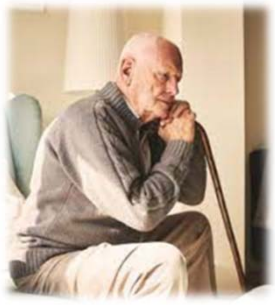
- Earlier mortality similar but febrile neutropenia, infections and average inpatient length of stay was higher for CPX-351

Matthews A, et al. ASH 2021.Abstract 795.

What do we take from this analysis? We take that there is two populations of patients out there. There are the older, more unfit, and there's the younger, more fit. Is there a difference in toxicities with these regimens? Yes, patients who received CPX-351, as we would expect, had a much higher rate of febrile neutropenia, documented infection, and almost three times the inpatient stay, as opposed to those that got the venetoclax/azacitidine. If you are to offer that, you probably need to select patients who are going to be able to tolerate that. Regardless of which patients were selected for which therapy, overall survival was the same. This suggests that, as clinicians, we are doing a good job of selecting the appropriate therapy for the appropriate patients based on all of this information that we have on prognostic factors. The important factor here was to get them through the induction chemotherapy with the potential for some of them to go to transplant.

Treatment Selection:
A Focus on Prognostic Indicators

Meet Our Patient



Patient Notes

- 71-year-old man presented with acute shortness of breath and fatigue
- WBC 22K (55% myeloblasts), hgb 6 gm/dl, platelets 34K
- PMHx: Prior MI s/p stents, hypertension, localized prostate ca (radiation only)

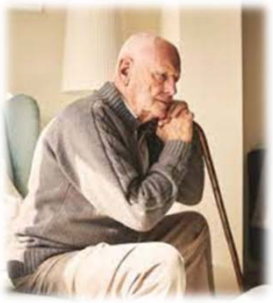
Physical Exam Findings: ECOG 1

- Easily fatigued man, appears stated age in no acute distress
- Clear lungs bilaterally with no wheezes or rales
- Heart rate tachycardic with regular rate and rhythm

Going back to the case presentation we talked about, the 71-year-old gentleman who had an ECOG performance status of one, with probably at least two, or three, or four comorbidities, what would this patient be considered? I would consider this patient to be falling into the unfit category based on their questionable comorbidities.

Treatment Selection:
A Focus on Prognostic Indicators

Meet Our Patient



Labs

- Normal renal and liver function
- Marrow shows 82% myeloblasts (MPO+) with Auer rods
- Karyotype: Complex karyotype (≥3 aberrations including del(17p)
- NGS: p53 mutation

Also, not so much their ECOG performance status, but potentially based on the fact that they have a poor karyotype AML with a p53 mutation. Although there are some factors, the ECOG performance status in particular, which would favor a more aggressive approach, the comorbidities and the overall impression incorporating the biological factors suggests that this patient may benefit from a lower intensity regimen with decreased toxicity.

Summary

- Limitations of clinical trial criteria used to differentiate patients who are “fit” versus “unfit” for intensive induction therapy
- Performance status in determining patient fitness for intensive therapy
- Other factors linked to therapeutic resistance: molecular, cytogenetics, MRD
- Impact of comorbidity status on outcomes in both high- and low-intensity treatment groups

As we talked about in summary, we've discussed some of the clinical trial criteria used to standardly differentiate patients into fit and unfit. We've talked about performance status, comorbidity. We've talked about the impact of the underlying biology, and we've talked a little bit about how we're doing this in the real world, with that ASH abstract showing us how clinicians are already differentiating intensity of therapy based on these factors.

I'd like to thank everybody for your attention. I hope this was a useful exercise and that this is going to help you as you move forward in selection of patients for future AML therapy.