# MDS in 2021 (and beyond)

Rena Buckstein

Chair, Hematology Site Group

Odette Sunnybrook Cancer Center

Associate Professor, Dept of Medicine, U of T

Toronto, Ontario

### Agenda

- Case
- Diagnosis and Prognosis
- Therapeutic algorithm
- New approved agents
- Clinical trials

### Case

- 71 yo male
- Retired teacher
- PMH: HTN, type 2 diabetes, osteoarthritis of his back
- Family history: no cancer
- Married with 2 grown children, 4 grandchildren
- Walks 1 hour daily
- Past smoker, ETOH social



### Case-continued

- Complains to GP of increasing fatigue over the last 2 months, decreased stamina, some SOB when climbing stairs
- No weight loss, infections, swelling, skin rashes or change in organ function
- Exam normal
- Blood work: hgb 105 (normal 135-175), WBC 3.5 (normal 5-10), Neutrophils are 1.5, platelets are 130 (normal 150-400)
- Referred to me- Bone marrow biopsy is performed
- Diagnosis is MDS: RCMD with ring sideroblasts; blasts are 3%
- Chromosomes are normal

### Case continued

- What is this diagnosis?
- What is his prognosis?
- Is it curable?
- What are his treatment options?

### Myelodysplastic syndromes

- Heterogenous group of blood cancers (clonal stem cell disorder)
- Incidence is 4/100,000
  - 8700 new cases each year in Canada
- More common in men
- May arise after previous chemotherapy or radiation or occupational exposures
- Presents with low blood counts, infections, bleeding
- 25-30% will develop acute myeloid leukemia
- Bone marrow transplant is the only cure





### Symptoms of MDS

- Fatigue
- Breathlessness
- Easy bruising or bleeding
- Weight loss
- Loss of stamina
- Asymptomatic

## Epidemiology



### **Risk factors**

- Unknown in 80%
- Age, male sex
- Mutagenic exposures:
  - Radiation
  - Chemotherapy
    - Alkylators: cyclophosphamide, melphalan
    - Topo-2 inhibitors: mitoxantrone, etoposide
- Environmental/occupational- heavy metals, benzene
- Smoking
- Autoimmunity
- Obesity (BMI > 25)
- Hereditary

### Diagnosis

- Bone marrow aspirate and biopsy
- Classification using WHO
  - How many blood lineages look abnormal
  - What % blasts
  - Chromosome del5q or other chromosome abnormalities
  - Are there ring sideroblasts



5q- Syndrome: Chromosomal Abnormality



del(5)(q13q33)

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### Prognosis

- IPSS
- IPSS-R
- IPSS-M
- Provide estimations of overall survival (years) and probability of developing AML

#### Prognostic Values for Determining IPSS-R Score

Value/Score	0	0.5	1	1.5	2	3	4
Cytogenetics Risk Group	Very Good		Good		Intermediate	Poor	Very Poor
Blasts (%)	<2%		>2%-<5%		5-10%	>10%	
Hemoglobin (g/dL)	≥10		8-<10	<8			
Platelets	≥100,000	50-<100,000	<50,000				
ANC	≥0.8	<0.8					

Cytogenetics play a very important role in estimating prognosis for a patient with MDS. The IPSS-R is based on a revised grouping of cytogenetic abnormalities (see: *IPSS-R calculator at www.mds-foundation.org/ipss-r-calculator*)

Cytogenetic Risk Group	Cytogenetic Abnormalities	Estimated Survival
Very Good	del(11q), -Y	5.4 years
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8 years
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones	2.7 years
Poor	-7, inv(3)/t(3q)/del(3q). double including -7/del(7q) Complex: 3 abnormalities	1.5 years
Very Poor	Complex: >3 abnormalities	0.7 years

There are five overall risk scores in the IPSS-R with estimated survival and median risk of AML:

Score	≤1.5 Very Low	>1.5-3 Low	>3-4.5 Intermediate	>4.5-6 High	>6 Very High
Overall Survival (mean)	8.8 years	5.3 years	3.0 years	1.6 years	0.8 years
Risk of AML in 25% of patients (median)	Not reached	10.8 years	3.2 years	1.4 years	0.73 years

Our patient: IPSS-R is 2: low risk

Uncoding the genetic heterogeneity of myelodysplastic syndrome	Pathways and	Frequency, %
	RNA Splicing	
	SF3B1	15–30
DNMI3A PPM1D IDH1 NRAS	SRSF2	10–20
KRAS	U2AF1	<10
	ZRSR2	<10
	DNA methylation	
	TET2	20–30
	DNMT3A	10–15
	IDH1/IDH2	5
	Chromatin	
SF3B1 FLT3	modification	15–20
SRSE2 NPM1	ASXL1	
ZRSR2 EZH2 RUNX1	EZH2	5
U2AF1 ASXL1 CATA2 BCOB	RAS pathway	
GATAZ BEOR	CBL	<5
Early — Late	NRAS/KRAS	<5
	Transcription	
R. Coleman Lindsley, Am Soc Hematol Educ Program, 2017, Figure 2.	RUNX1	10
	BCOR	<5
	Tumor suppressor	
	ТР53	5



Papaemmanuil E et al. Blood (2013) Haferlach T et al., Leukemia (2014)



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Rafael Bejar Haematologica 2014;99:956-964

Category	Variable
confounder	1/10 Age, in years
	Sex Male
	Type Secondary/Therapy-related
clinical	15 Bone Marrow Blasts, in %
	Visa min(Platelets.250), in x10 <sup>8</sup> /L
	Hemoglobin, in gidL
cytogenetics	IPSS-R category vector*
gene main effects	TP53 <sup>null</sup>
22 variables, 21 genes	MLL <sup>PTD</sup>
	FLT3 <sup>ID-HD</sup>
	SF381"
	NPM1
	RUNXI
	IDH2
	NRAS
	ETV6
	EZH2
	SETBP1
	CBL
	SRSF2
	UZAF1
	DNMT3A
	ASXL1
	KRAS
	NFI
	STAG2
	BCOR
	CEBPA
	SF361"
gene residuals <sup>3</sup> 1 variable, 17 genes	min(Nres,2)

# Patient tailored risk score



### **IPSS-M risk strata**



### IPSS-R score of > 3.5 distinguishes lower from higher risk disease



# Other prognostic factors

- Fatigue
- Frailty
- Disability
- Comorbidity

Refine prognosis further by 20-30%

### Goals of Treatment

#### Lower risk disease

- Improve BM function
- Decrease or eliminate transfusions
- Improve quality of life
- Improve overall survival

#### **Higher risk disease**

- Delay time to acute leukemia
- Improve overall survival
- Improve quality of life
- Decrease or eliminate transfusions

### **Anemia Management Algorithm in LR-MDS**



Volpe. Ther Adv Hematol. 2021;12:2040620720986641.

### **Treatment Algorithm: Higher-Risk MDS**



#### Luspatercept's Novel Mechanism Restores RBC's Ability to Mature

ACCELERON



8

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

P. Fenaux, U. Platzbecker, G.J. Mufti, G. Garcia-Manero, R. Buckstein, V. Santini, M. Díez-Campelo, C. Finelli, M. Cazzola, O. Ilhan, M.A. Sekeres, J.F. Falantes, B. Arrizabalaga, F. Salvi, V. Giai, P. Vyas, D. Bowen, D. Selleslag, A.E. DeZern, J.G. Jurcic, U. Germing, K.S. Götze, B. Quesnel, O. Beyne-Rauzy, T. Cluzeau, M.-T. Voso, D. Mazure, E. Vellenga, P.L. Greenberg, E. Hellström-Lindberg, A.M. Zeidan, L. Adès, A. Verma, M.R. Savona, A. Laadem, A. Benzohra, J. Zhang, A. Rampersad, D.R. Dunshee, P.G. Linde, M.L. Sherman, R.S. Komrokji, and A.F. List

ABSTRACT

### MEDALIST: Study Design

• International, randomized, double-blind, placebo-controlled phase III trial



Patients ≥ 18 yrs of age with nondel(5q) MDS and ring sideroblasts per WHO 2016 criteria; IPSS-R risk that is very low, low, or intermediate; refractory, intolerant, or ineligible for ESAs; RBC transfusion dependent (N = 229)



Treatment continued until lack of clinical benefit or PD

- Primary endpoint: RBC-TI for  $\geq$  8 wks between Wk 1 and Wk 24
- Secondary endpoints: RBC-TI for ≥ 12 wks between Wk 1 and Wk 24, modified hematologic improvement–erythroid response per IWG 2006 criteria, DoR, Hb change from baseline

#### RBC-TI $\geq$ 8 weeks Achieved any time during treatment period



- Primary endpoint previously reported: 37.9% luspatercept versus 13.2% placebo patients achieved RBC-TI ≥ 8 weeks during Weeks 1–24 (P < 0.0001)<sup>1</sup>
- Secondary endpoint : 52.9% luspatercept versus 11.8% placebo patients achieved modified HI-E responses per IWG 2006 criteria

CI, confidence interval; OR, odds ratio.

Data cutoff: July 1, 2019.

1. MEDALIST authors. Blood. 2018;132:abstract 1.

### Luspatercept



### Over 48 weeks: 12 fewer units of blood and 6 fewer transfusions

### How is luspatercept given?

- Under the skin, every 3 weeks
- 3 dose escalations 6 weeks (1, 1.33, 1.75 mg/kg)

# Side effects of luspatercept

	Luspatercept (N=153)	Placebo (N=76)
System Organ Class/Preferred Term	Any Grade, n (%)	Any Grade, n (%)
General disorder or administration-site condition		
Fatigue <sup>a</sup>	70 (46)	19 (25)
Gastrointestinal disorder		
Diarrhea	34 (22)	7 (9)
Nausea <sup>b</sup>	31 (20)	6 (8)
Constipation	17 (11)	7 (9)
Nervous system disorder		
Dizziness	30 (20)	4 (5)
Headache	24 (16)	5 (7)
Syncope/presyncope	10 (7)	1 (1)
Renal and urinary disorders		
Renal impairment <sup>b,c</sup>	11 (7)	2 (3)

# Side Effects of Luspatercept

	Luspatercept (N=153)	Placebo (N=76)
Organ System Class/Preferred Term	Any Grade, n (%)	Any Grade, n (%)
Musculoskeletal or connective-tissue disorder		
Back pain <sup>a</sup>	29 (19)	5 (7)
Myalgia	13 (8)	5 (7)
Infection or infestation		
Bronchitis <sup>a</sup>	17 (11)	1 (1)
Urinary tract infection <sup>a</sup>	17 (11)	4 (5)
Upper respiratory tract infection	15 (10)	3 (4)
Viral upper respiratory tract infection	12 (8)	4 (5)
Influenza	10 (7)	0 (0)
Vascular Disorders		
Hypertension <sup>b</sup>	13 (9)	7 (9)

# Other agents for transfusion dependent lower risk MDS

- Imetelstat
- Roxadustat
- Decitabine-cedazuridine

## Imetelstat : A first-in-class telomerase inhibitor



Parameter	Subset (n=38)
8 week TI	42%
Median time to onset	8.3 weeks
Median duration of TI	86 weeks
HI-E (IWG 2006)	68%

Platzbecker U et al. EHA 2020. Abstract S183. Steensma D et al. JCO 2021.

### HIFa prolyl hydroxylase domain inhibitor: Roxadustat



#### Roxadustat Transfusion Independence at 28 and 52 Weeks (Combined Data)



 During first 8 wks of fixed-dose treatment, transfusion independence achieved by 25% of patients receiving roxadustat 1.5 mg/kg and 50% of patients receiving roxadustat 2.0 mg/kg

Henry. ASH 2020. Abstr 1277. Reproduced with permission.

- 58% had reduction in RBC transfusions of > 50%
- Ongoing phase III study versus placebo (n=156)

### Hypomethylating agents are effective in MDS



#### **DNA methyltransferases in MDS**

Azacytidine: 75 mg/m2 SC x 7 days Decitabine: 20 mg/m2 IV x 5 days

### Inqovi: Decitabine + Cedazuridine



### **DEC-C Phase 3: Randomized Crossover Design<sup>1,2</sup>**



### **DEC-C Phase 3: Patient Baseline Characteristics<sup>1</sup>**

Characteristics		Total Treated N=133 (n%)	
Median age, y (range)	Median age, y (range)		
Sar	Male	e 87 (65%)	
Sex	Female	46 (35%)	
Median weight, kg (range)		83 (45 -158)	
Median BSA, m² (range)		1.98 (1.4 - 2.9)	
CMML		16 (12%)	
	High risk	21 (16%)	
MDS, IPSS classification	Int-1 and 2	90 (68%)	53% lower risk
	Low risk	6 (5%)	<b>L</b> 36% nigher risk
	RBCs	53 (39%)	
Transfusion dependent	Platelets	12 (9%)	
ECOG PS	0	55 (41%)	
	1	78 (59%)	

~7.5% of patients had received prior HMAs: Decitabine/Azacitidine; ( $\leq 1$  cycles)

1. Clinical Efficacy and Safety of Oral Decitabine/Cedazuridine in 133 Patients with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML), Michael R. Savona et al, Session 637, Abstract # 1230 presented at the ASH Virtual Annual Meeting, Dec 5 – 8, 2020

### Phase - 3 Results: AUC equivalence, Demethylation<sup>1</sup>

DEC			IV DEC	DEC-C		Ratio of Geo. LSM	Intrasubject	
5-day AUC <sub>0-2</sub>	₂₄ (h∙ng/mL)	Ν	Geo. LSM	Ν	Geo. LSM	Oral/IV, % (90% CI)	(%CV)	
Primary Analysis	Paired*	123	864.9	123	855.7	98.9 (92.7, 105.6)	31.7	

Geo. LSM = Geometric Least Squares Means





### **Results Phase-3: Efficacy Response<sup>1</sup>**

Response category	Treated Patients (N=133), n (%)	95% CI	Median time to	Median
Complete response (CR)	29 (22%)	(15.1,29.8)		(months)
Partial response (PR)	0			(montins)
Marrow CR (mCR)	43 (32.3%)	(24.5,41.0)	Time to CR	4.5
mCR with hematologic improvement	22 (16.5%)	(10.7,24.0)	Time to marrow	2.2
Hematologic improvement (HI)	10 (7.5%)	(3.7,13.4)	CR	
HI-erythroid	2 (1.5%)	(0.2,5.3)	Duration of CD	140
HI-neutrophils	1 (0.8%)	(0.0,4.1)	Duration of CR	14.0
HI-platelet	7 (5.3%)	(2.1,10.5)	Duration of best	12.7
Overall response (CR + PR + mCR + HI)	82 (61.7%)	(52.8,69.9)	response	
Progressive Disease	6 (4.5%)	(1.7,9.6)	• 34 (26%) of subjects pro	ceeded to HCT
No Response	28 (21.1%)	(14.5, 29.0)	Transfusion independen	ce (RBC and or
Non-evaluable	17 (12.8%)	(7.6, 19.7)	platelets): 30/50 (53%) <sup>2</sup>	
Clinical Efficacy and Safety of Oral Decitabine/Cedazuridine in 133 Patients with Myelodysplastic Syndrom (MDS) and Chronic Myelomonocytic Leukemia (CMML), Michael R. Savona et al, Session 637, Abstract # 1230 presented at the ASH Virtual Annual Meeting, Dec 5 – 8, 2020 INQOVI (decitabine/cedazuridine) tablets [product monograph]. Oakville, ON: Taiho Pharma Canada, Inc;	nes		Median number of cycle	es: 9 <sup>3</sup>
July 03, 2020 Prolonged Survival Observed in 133 MDS Patients Treated with Oral Decitabine/Cedazuridine Michael R				

 Prolonged Survival Observed in 133 MDS Patients Treated with Oral Decitabine/Cedazuridine, Micha Savona et al, Abstract P648, © Poster presented at: 16th International Congress on Myelodysplastic Syndromes (MDS), virtual meeting, September 23 26, 2021

1.

2.

TAIHO PHARMA CANADA, INC.

### **Results Phase-3: Overall Survival<sup>1</sup>**



- Median follow up is 32 months
- mOS for the 133 patients is 31.7months (95% CI: 28.0, NE).
  - mOS for higher risk disease: 15 months
- Leukemia free survival is 29.1 months (95% CI:22.1, NE)

1. Prolonged Survival Observed in 133 MDS Patients Treated with Oral Decitabine/Cedazuridine, Michael R. Savona et al, Abstract P648, © Poster presented at: 16th International Congress on Myelodysplastic Syndromes (MDS), virtual meeting, September 23 26, 2021

### Safety of decitabine/cedazuridine

# Table 3. Results: Safety - Treatment Emergent Adverse Events in >10% of Patients\*

Preferred Term	Phase 3 Total (N=133, n [%])	Phase 3 Total Grade 3 or higher					
Neutropenia	68 (51%)	65 (49%)					
Thrombocytopenia	71 (53%)	62 (47%)					
Anaemia	55 (41%)	47 (35%)					
Leukopenia	33 (25%)	29 (22%)					
Febrile	18 (14%)	17 (13%)					
Neutropenia							
Fatigue	32 (24%)	3 (2%)					
Diarrhea	22 (17%)	2 (2%)					
Nausea	33 (25%)	0 (0%)					
Decreased	19 (14%)	0 (0%)					
Appetite							
Constipation	18 (14%)	0 (0%)					
*Events attributable to oral decitabine/cedazuridine							

- Safety profile consistent with that of IV decitabine.
- No new safety concerns with longer follow up.

### Which HMA to use for higher risk disease?

### SEER Medicare study 2004-2011



Median OS 15 mos

Median OS 11 months

Zeidan A et al. BJH 2016

### Advantages and Disadvantages: AZA

#### Advantages

- Known survival benefit
- Not too tough on the blood counts
- Can be used as bridge to transplant
- May achieve RBC transfusion independence in 40%
- Flexibility in dose adjustment

#### Disadvantages

- Can take 6 cycles to work
- Requires regular in person visits
- Not funded for lower risk disease

### Advantages and Disadvantages of DEC-C

### Advantages

- Oral
- Works quickly to reduce blasts
- May be used as bridge to transplant
- Achieves RBC transfusion independence in 50%
- Available for lower risk disease

#### Disadvantages

- No randomized trial for OS benefit
- Unclear if equivalent to AZA
- More suppressive of blood counts at the beginning
- Less flexibility in dose adjustment
- Not yet funded

### Select Current Phase III Clinical Trials for Newly Diagnosed High Risk MDS

	Sabatolimab	Tamibaterone	Magrolimab	Venetoclax
		RARU agomsi-		
Current Status	Ongoing	Ongoing	ENHANCE recruiting	VERONA recruiting
Population	Intermed High Very high CMML-2	RARα + Intermed High Very high	Intermed High Very high	Intermed High Very high
Planned "n"	500	190	520	500
Comparator	AZA + PBO	AZA + PBO	AZA + PBO	AZA + PBO
Dosing of IP (PLUS SOC AZA)	IV q4 weeks	Oral D8-28	C1:D1,4,8,11,15, 22 C2: D1, 8, 15, 22 ≥C3 Q2W	Oral D1-14
Endpoint	OS	CR	CR and OS	CR and OS

# Allo vs Hypomethylating/Best Supportive Care in MDS (BMT CTN 1102)

- Open-label, multicenter, biologic assignment study
- Assignment based on high-resolution typing to identify 8/8 HLA-matched related or unrelated donors
  - Mismatched, haploidentical and umbilical cord blood excluded
  - Donor arm subjects expected to undergo HCT within 6 months
- Subjects: Randomized 260 = Donor; 124 No Donor
  - Age 50-75
  - Primary MDS with intermediate-2 or high risk by IPSS
  - Candidates for traditional reduced-intensity transplantation
  - Transplant/non-transplant therapy per institutional standards



### Summary

- MDS is a disease of the myeloid blood stem cell that leads to bone marrow failure and a propensity to AML
- Life expectancy is truncated by the disease
- Treatment is geared according to risk score
- Many patients receive supportive care with transfusions
- Allogeneic transplant is the only potential cure (< 10% qualify)
- Oral hypomethylating agent are now available
- Luspatercept is approved for patients with RS who are TD and will reduce or eliminate transfusions in > 50% of patients who have already received ESAs.
- Numerous clinical trials are underway



### Mds-foundation.org



#### **Building Blocks of Hope Downloads**

#### **Download Complete Book**





# You and MDS – An Animated Patient's Guide to Myelodysplastic Syndromes



We are excited to announce the MDS Foundation's new online patient education resource, titled "You and MDS: An Animated Patient's Guide to Myelodysplastic Syndromes". Please click here to be directed to the You and MDS resource.

TYPES THERAPEUTICS CONGRESSES TRIALS EXPERT OPINIONS