FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Clinica e Terapia delle Sindromi Mielodisplastiche

28 maggio 2022

Ottimizzazione del trattamento con ipometilanti

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Current treatment options in HR-MDS include HMA and Allo-SCT

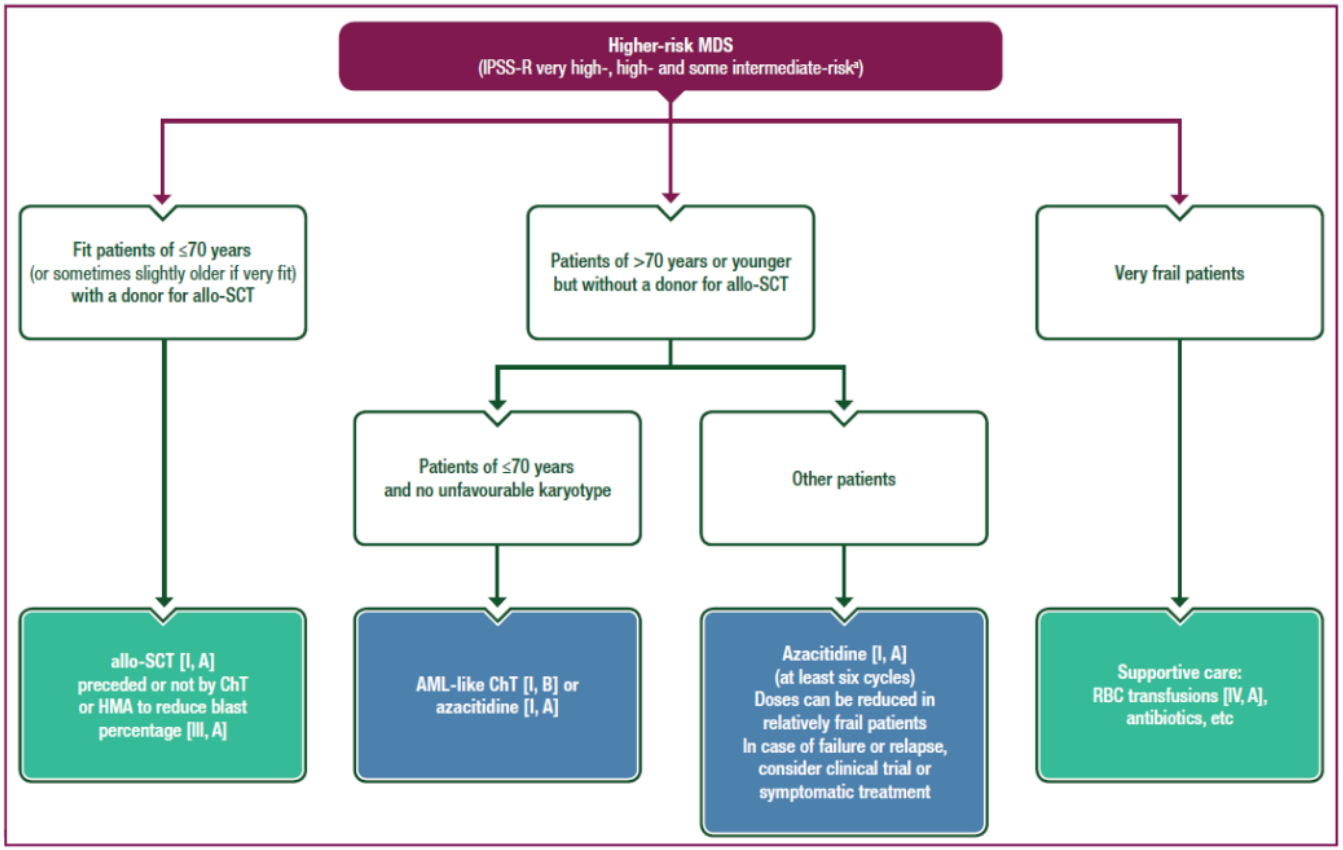

Figure 2. Treatment algorithm for higher-risk MDS.
allo-SCT, allogenic stem cell transplant; AML, acute myeloid leukaemia; ChT, chemotherapy; HMA, hypomethylating agent; IPSS-R, revised international prognostic scoring system; MDS, myelodysplastic syndromes; RBC, red blood cell.
[a] For IPSS-R intermediate-risk MDS patients, whether they should initially receive treatment for lower-risk MDS or higher-risk MDS is also based on other factors including age, comorbidities, importance of cytopaenias, somatic mutations, effect of first-line treatment, etc.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†☆

P. Fenaux[1,2], D. Haase[3], V. Santini[4], G. F. Sanz[5,6], U. Platzbecker[7] & U. Mey[8], on behalf of the ESMO Guidelines Committee*

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Available online 19 November 2020

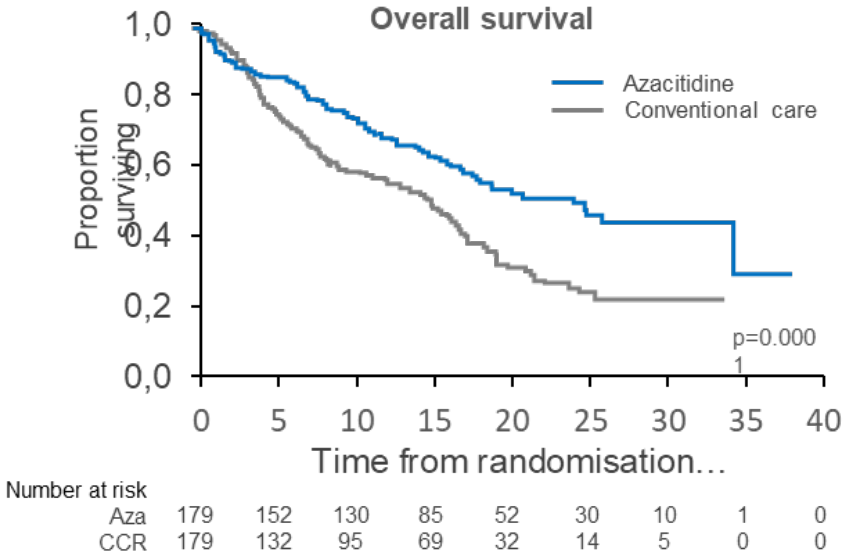
Hypomethylating agents. Hypomethylating agents (azacitidine, decitabine) offer an alternative to intensive treatment in high-risk MDS. They are not curative but may result in transfusion independence, improved QoL and survival benefit and are well tolerated in the elderly and in patients with comorbidities.

Recommendations

- Azacitidine is recommended in patients with higher-risk MDS without major comorbidities not immediately eligible for allo-SCT [I, A].
- Reducing the marrow blast count before allo-SCT with AML-like ChT or HMAs is generally considered when marrow blasts are ≥10%, especially for non-myeloablative allo-SCT [III, A].

Current HR-MDS treatment options for unfit patients are limited to HMAs, including azacitidine

Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk MDS: a randomised, open-label, phase III study (AZA-001)



Total ITT (n=358)	Azacitidine (n=179)	CCR* (n=179)	p value†
Haematological response			
Any remission	51 (29%)	21 (12%)	0.0001
Complete remission	30 (17%)	14 (8%)	0.015
Partial remission	21 (12%)	7 (4%)	0.0094
Stable disease	75 (42%)	65 (36%)	0.33
Haematological improvement‡			
Any improvement	87/177 (49%)	51/178 (29%)	<0.0001

After a median follow-up of 21.1 months, **median overall survival was 24.5 months** for the azacitidine group vs **15.0 months** for the CCR group (HR: 0.58; 95% CI 0.43–0.77; p=0.0001)

Grade 3/4 toxicity azacitidine vs CCR: neutropenia 91% vs 76%; thrombocytopenia 85% vs 80%; anaemia 57% vs 68%

*Best supportive care, low-dose cytarabine, or intensive chemotherapy as selected by investigators before randomisation. †p value from Fisher's exact test for comparing patients with response between the azacitidine group and the combined group of CCR, or within investigator preselection, between azacitidine and the individual CCR.
‡Haematological improvement can include complete and partial remission
CCR, convention care regimen; CI, confidence interval; HMA, hypomethylating agent; HR, hazard ratio; ITT, intention to treat; MDS, myelodysplastic syndromes
Fenaux P, et al. Lancet Oncol 2009;10:223–232

Courtesy by M. Della Porta

Azacitidine clinical studies in HR-MDS 2021 update

Leukemia Research 104 (2021) 106555

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Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

A systematic review of higher-risk myelodysplastic syndromes clinical trials to determine the benchmark of azacitidine and explore alternative endpoints for overall survival

Jacqueline S. Garcia[a,*], Ronan T. Swords[b], Gail J. Roboz[c], Meagan A. Jacoby[d], Guillermo Garcia-Manero[e], Wan-Jen Hong[f], Xiaoqing Yang[b], Ying Zhou[b], Uwe Platzbecker[g], David P. Steensma[a], Johannes E. Wolff[b], Pierre Fenaux[h]

- A systematic literature search and study-level systematic review of 237 clinical studies with 10.119 HR-MDS patients treated with azacitidine monotherapy
- Pooled marrow CR was 9% (N = 2.654); CR rate was 17 % (N = 6.943)
- Median OS was 18.6 months (N = 2.820)

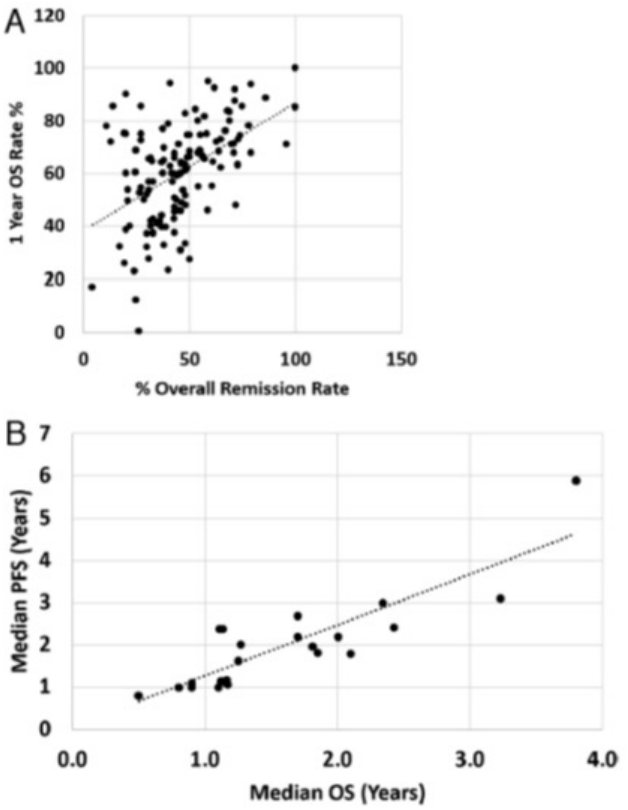


Fig. 1. (A) Overall remission rate had low correlation with 1-Year OS rate. N = 133; Pearson's Correlation Coefficient r = 0.493; $P = 1.6 \times 10^{-9}$. OS, overall survival. (B) mPFS correlates with mOS, but this outcome is rarely reported. N = 42 patient cohorts; Pearson's Correlation Coefficient r = 0.876; $P = 3 \times 10^{-14}$. PFS, progression-free survival.

Real-world evidence with azacitidine have shown consistently shorter median OS compared with AZA-001

Study	Patients treated with HMA, n	Median OS, months	Reference
Dutch azacitidine compassionate named patient programme	90*	13.0	van der Helm LH, et al. Br J Haematol 2011;155:599–606
Spanish Registry	251†	13.4	Bernal T, et al. Leukemia 2015; 29:1875–1881
GFM	282†	13.5	Itzykson R, et al. Blood 2011;117:403–411
Hellenic MDS Study Group	353†	13.0	Papageorgiou SG, et al. Hematol Oncol 2018;36:693–700
Hematology, Sapienza University, Italy	110	19.2	Scalzulli E, et al. Ann Hematol 2019; 98:1919–1925

In AZA-001, median overall survival was 24.5 months for the azacitidine group[1]

*Patients with MDS, CMML, and AML were included in the analysis. †Patients with higher-risk MDS were included in the analysis
CMML, chronic myelomonocytic leukaemia; GFM, Groupe Francophone des Myelodysplasies; HMA, hypomethylating agent; MDS, myelodysplastic syndromes; OS, overall survival

1. Fenaux P, et al. Lancet Oncol 2009;10:223–232

Courtesy by M. Della Porta, modified

Resistance/sensitivity to HMA (heterogeneity of response/outcome)

Clinical/Individual factors

Disease related factors

Cytogenetics
Somatic mutations
DNA methylation pattern baseline
Drug metabolizing enzyme expression
Others.....

Courtesy by Valeria Santini, modified

Table 1

Epidemiologic and clinical/hematological factors found to affect prognosis of patients with MDS, eligibility for treatment with hypomethylating agents and treatment response.

Factor	Effect on prognosis	Effect on eligibility for treatment with HMAs and treatment response
Gender	Male gender – survival disadvantage [13,14,15] Young high-risk females – unfavorable prognosis [14]	Female patients – better response to decitabine than 5-azacytidine [16]
Age	IPSS-RA – prognostic impact mainly in lower risk patients [17]	5-azacytidine effective and safe in patients >75 years [18] and >80 years [19] Comprehensive geriatric assessment detects health issues predicting poor survival in patients treated with 5-azacytidine [20]
Anemia	Additive prognostic value to IPSS [23] Transfusion dependence has a detrimental effect on prognosis [3,24,25]	
Thrombocytopenia	Predictive of poor OS [26]	Not predictive or response to 5-azacytidine [26]
Neutropenia	Correlated with lower OS [27]	
Monocytopenia	Correlated with lower OS in univariate analysis [28]	
Circulating blasts	Independent prognostic factor for OS in patients treated with 5-azacytidine [29]	
Comorbidities	MDS-CI used to detect patients with worse prognosis [32] An eGFR<45 ml/min/1.73m2 increases the predictive value of IPSS-R in patient treated with 5-azacytidine [36]	MDS-CI useful in identifying patients' chances to respond to 5-azacytidine [23] 5-azacytidine administration feasible in patients with CKD [33,34,35]

HMAs, hypomethylating agents; IPSS-RA, age adjusted international prognostic scoring system; OS, overall survival; MDS-CI, MDS comorbidity index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

Previous therapy, marrow fibrosis grade 3, hypocellular bone marrow

Diamantopoulos and Viniou, Leuk Res 2021

Prognostic factors for response and OS in Int-2/High-risk MDS patients treated with AZA

GFM ATU compassionate use study (n = 282)

AZA response score

Variable	Response rate, yes/no %	p value*
Prior LD ARA-C	24/46	0.009
Normal karyotype	51/39	0.003
Marrow blasts > 15%	35/50	0.004
Response duration		
Complex karyotype	4.6 vs 10.3 months	0.0003

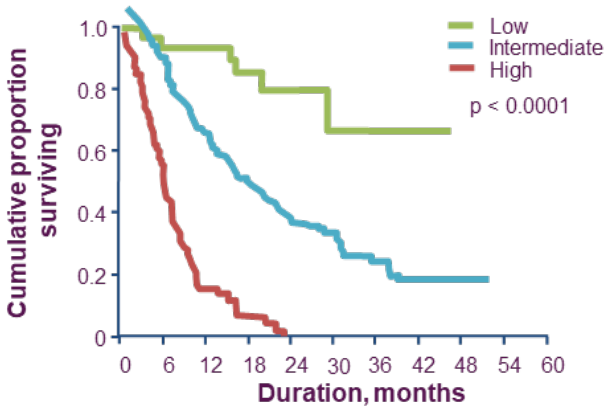
* Multivariate analysis.
ATU, authorization for temporary use.

Itzykson R, et al. Blood. 2011;117:403-11.

OS prognostic score

Variable	Score
Performance status ≥ 2	1
Circulating blasts	1
RBC transfusion dependence ≥ 4 U/8 wks	1
Intermediate karyotype	1
High-risk karyotype	2

Low: 0
Intermediate: 1–3
High: 4–5



Clinical factors predicting outcome in MDS treated with HMAs

Annals of Hematology (2019) 98:1919–1925
https://doi.org/10.1007/s00277-019-03724-9

ORIGINAL ARTICLE

Check for updates

Identification of predictive factors for overall survival at baseline and during azacitidine treatment in high-risk myelodysplastic syndrome patients treated in the clinical practice

Emilia Scalzulli[1] · Matteo Molica[1] · Danilo Alunni Fegatelli[2] · Gioia Colafigli[1] · Lorenzo Rizzo[1] · Marco Mancini[1] · Fabio Efficace[3] · Roberto Latagliata[1] · Robin Foà[1] · Massimo Breccia[1]

- 110 MDS patients (IPSS intermediate 2/high) treated outside of clinical trials at a single institution between September 2003 and January 2017.
- No differences in terms of OS were observed with regard to gender and age at baseline (< 65 years, 65–75, and > 75 years).
- According to the IPSS-R, the very high-risk group had an inferior 2-year OS (17%) compared with intermediate-group patients (64%, p < 0.001).
- Transfusion independency at baseline was identified as a favorable prognostic factor on 1-year (66.8%) and 2-year OS (43.4%) (p < 0.001).
- After four cycles, the persistence of bone marrow blasts > 10% identified patients with a worse outcome, with a 2-year OS of 9.4% (p=0.002).
- The occurrence of an infection during the first four cycles impacted on the 2-year OS (31.6% vs 58.3% in patients without infections, p = 0.032).
- Patients receiving at least 24 cycles of the drug have a 5-year OS of 38.2%.

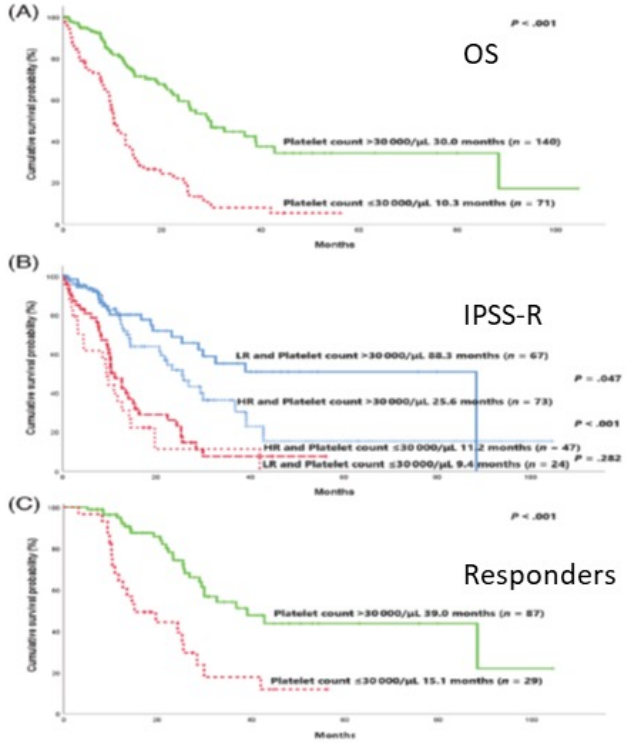


FIGURE 1 Survival outcome of patients according to the limit of 30 000/µL at treatment initiation with HMA: A, Overall survival; B, IPSS-R risk stratification; C, Subgroup of responders. Kaplan Meir plots and log-rank test; n, number of patients; HR, high risk; LR, low risk; NR, not reached

Received: 2 July 2020 | Revised: 26 August 2020 | Accepted: 27 August 2020
DOI: 10.1002/ajh.25987

Severe thrombocytopenia as a predictor of survival and response to hypomethylating agents in myelodysplastic syndromes: A Latin-American cohort of 212 patients

Lazzarino C et a, Ann Hematol 2020

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Can we predict response to HMAs?

Comparison of risk stratification tools in predicting outcomes of patients with higher-risk MDS treated with HMAs (N=632)

IPSS			IPSS-R			FPSS			MDAPSS			WPSS		
Risk group	n (%)	ORR (%)	Risk group	n (%)	ORR (%)	Risk group	n (%)	ORR (%)	Risk group	n (%)	ORR (%)	Risk group	n (%)	ORR (%)
Low	0 (0)	-	Very low*	0 (0)	-	Low	40	57.5	Low*	10 (1.6)	70.0	Very low*	1 (0.1)	0.0
INT-1	0 (0)	-	Low	6 (0.9)	50.0	INT	490 (77.6)	41.4	INT-1	54 (8.5)	37.0	Low*	5 (0.8)	40.0
INT-2	440 (69.6)	39.8	INT	68 (10.8)	48.5	High	102 (16.1)	39.2	INT-2	184 (29.1)	43.5	INT	20 (3.2)	40.0
High	192 (30.4)	43.1	High	213 (33.7)	37.6				High	384 (60.8)	41.4	High	323 (51.1)	42.4
			Very high	345 (54.6)	43.4							Very high	273 (43.2)	42.5
												N/A†	10 (1.6)	30.0
		p=0.51			p=0.39			p=0.24			p=0.46			p=0.93

No prognostic tool predicts the probability of achieving an objective response

*Not estimable owing to small cell count. †Only patients with specific WHO classifications could have a WPSS score calculated. Patients who had an ineligible WHO classification were grouped into a 'Not Applicable' category so they would not be excluded from the sample
FPSS, French Prognostic Scoring System; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; IPSS-R, revised International Prognostic Scoring System; MDAPSS, MD Anderson Prognostic Scoring System; MDS, myelodysplastic syndromes; N/A, not applicable; ORR, overall response rate; WPSS, World Health Organization classification-based Prognostic Scoring System
Zeidan AM, et al. Leukemia 2016;30:649–657

Courtesy by M. Della Porta

Cabezón et al. Clin Epigenet (2021) 13:9
https://doi.org/10.1186/s13148-021-01002-y

Clinical Epigenetics

RESEARCH Open Access

Different methylation signatures at diagnosis in patients with high-risk myelodysplastic syndromes and secondary acute myeloid leukemia predict azacitidine response and longer survival

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Abstract

Background: Epigenetic therapy, using hypomethylating agents (HMA), is known to be effective in the treatment of high-risk myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) patients who are not suitable for intensive chemotherapy and/or allogeneic stem cell transplantation. However, response rates to HMA are low and

EBioMedicine 31 (2018) 174–181

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journal homepage: www.ebiomedicine.com

Research Paper

Prognostic Role of Gene Mutations in Chronic Myelomonocytic Leukemia Patients Treated With Hypomethylating Agents

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OPEN

Gene expression signatures associated with sensitivity to azacitidine in myelodysplastic syndromes

young Choi[5], Hye Joung Kim[4], Yong-Rim Kwon[6], Vin Kim[1,2,3,9✉] & Yoo-Jin Kim[4,6,8,9✉]

rently the only curative treatment option for ansplant debulking treatment have been employed for d that marrow response (blast ≤ 5%) following the bridging an independent favorable factor for survival; however, it d to hypomethylating agent and which genomic features performed RNAseq for 23 MDS patients among which 14 w complete remission and primary resistance to azacitidine, d analyses of treatment-naive, baseline gene expression representing mitochondria and apoptosis were up-regulated snes involved in the Wnt pathway were relatively ndent validation cohorts of MDS patients, the expression d responders distinguished the patients with favorable line highlighting the prognostic and predictive implication. entified genes involved in ubiquitination, such as *UBC* he regulation of differential gene expression in treatment gether, identifying the gene expression signature may lar mechanisms of azacitidine and may also serve to predict

Leukemia Research 80 (2019) 11–18

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journal homepage: www.elsevier.com/locate/leukres

Mutations in the DNA methylation pathway predict clinical efficacy to hypomethylating agents in myelodysplastic syndromes: a meta-analysis

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ARTICLE INFO

Keywords:
Myelodysplastic syndromes
DNA methylation pathway
Mutational profile
Hypomethylating agents

ABSTRACT

Purpose: Myelodysplastic syndromes (MDS) are characterized by variable degrees of clinical outcomes. Until now, hypomethylating agents (HMAs) are the only drugs that have been approved by FDA in remedying this complicated prognosis disease, but without satisfactory outcome. So, biomarkers of better clinical outcome are of great significance. Many studies have already reported the potential prognostic value of DNA methylation pathway related gene (TET2/DNMT3 A/IDH) mutations in demethylation therapy patients, with controversial results. Therefore, a meta-analysis was performed to investigate their prognostic impact on HMAs treated MDS.
Methods: Databases, including PubMed, Embase, web of science and the Cochrane Library, were searched for relevant studies published up to 29 May 2018. Overall response rate (ORR) and overall survival (OS) were selected as endpoints. We extracted odds ratio to evaluate the effect of mutations on ORR, and the corresponding hazard ratios and their 95% confidence intervals for OS.
Results: A total of 13 cohort studies, covering 1398 patients with MDS treated by HMAs were included in the final meta-analysis. Our results indicated that DNMT3 A mutations had a favorable impact (P = 0.008) and TET2 mutations, which showed no significance (P = 0.06) in all included patients, could imply good efficacy in some subgroups on ORR. However, none advantages of mutations on ORR translated into a benefit in overall survival.
Conclusions: This meta-analysis indicates one favorable factor, DNMT3 A mutations, on ORR in MDS patients with HMAs therapy. The identification of mutations in DNMT3 A can improve clinical efficacy and help make treatment decisions.

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 34

Research Paper

Somatic mutations predict outcomes of hypomethylating therapy in patients with myelodysplastic syndrome

Seung-Hyun Jung[1,*], Yoo-Jin Kim[2,*], Seon-Hee Yim[1], Hye-Jung Kim[2], Yong-Rim Kwon[2], Eun-Hye Hur[3], Bon-Kwan Goo[3], Yun-Suk Choi[3], Sug Hyung Lee[4], Yeun-Jun Chung[1], Je-Hwan Lee[3]

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Je-Hwan Lee, ***email:*** *jhlee2@amc.seoul.kr*

Keywords: *myelodysplastic syndro*
Received: *January 12, 2016*

ABSTRACT

Although hypo risk myelodysplast unresolved issue. V and survival in MD (57 responders an (median depth of In multivariate ana HMT, but a lower h platelet count (<50 of poor response t mutation was signi consistent in multi overall survival, mu and *TP53* (*P*=0.008 VH, *P*=0.026) were survival, mutations and two clinical va independent predi and clinical predict azacitidine, overall became worse signi prognosis predictio

tic mutations contribute to the heterogeneous progn
methylating agents (HMAs) are active in CMML, but
cting response or survival. We analyzed a retrospecti
median of 7 cycles of azacitidine (n = 68) or decitabi
were available for all patients, from Sanger (n = 68
nse rate (ORR) was 52%, including complete response
mutations predicted a lower ORR (Odds Ratio [OR] =
ted a higher CR rate (OR = 1.38, p = 0.011) independ
7 months, overall survival (OS) was 23.0 months. In n
= .011), CBL^mut (HR = 1.90, p = 0.03) genotypes an
identify predicted worse OS while the *TET2*^mut/*ASXL1*^mut
lc scores CPSS and GFM had limited predictive powe
IA activity in CMML and for novel treatment strategi
T mutations.

www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 45), pp: 27882-27894

Clinical Review

Efficacy of azacitidine is independent of molecular and clinical characteristics - an analysis of 128 patients with myelodysplastic syndromes or acute myeloid leukemia and a review of the literature

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Keywords: *myelodysplastic syndromes; azacitidine; hypomethylating agents; response prediction; targeted therapy*
Received: *January 10, 2018* ***Accepted:*** *March 24, 2018* ***Published:*** *June 12, 2018*

ABSTRACT

Azacitidine is the first drug to demonstrate a survival benefit for patients with MDS. However, only half of patients respond and almost all patients eventually relapse. Limited and conflicting data are available on predictive factors influencing response. We analyzed 128 patients from two institutions with MDS or AML treated with azacitidine to identify prognostic indicators. Genetic mutations in *ASXL1, RUNX1, DNMT3A, IDH1, IDH2, TET2, TP53, NRAS, KRAS, FLT3, KMT2A-PTD, EZH2, SF3B1,* and *SRSF2* were assessed by next-generation sequencing.

With a median follow up of 5.6 years median survival was 1.3 years with a response rate of 49%. The only variable with significant influence on response was del(20q). All 6 patients responded (*p* = 0.012) but survival was not improved. No other clinical, cytogenetic or molecular marker for response or survival was identified. Interestingly, patients from poor-risk groups as high-risk cytogenetics (55%), t-MDS/AML (54%), TP53 mutated (48%) or relapsed after chemotherapy (60%) showed a high response rate. Factors associated with shorter survival were low platelets, AML vs. MDS, therapy-related disease, *TP53* and *KMT2A-PTD*. In multivariate analysis anemia, platelets, *FLT3*-ITD, and therapy-related disease remained in the model. Poor-risk factors such as del(7q)/-7, complex karyotype, *ASXL1, RUNX1, EZH2,* and *TP53* did not show an independent impact. Thus, no clear biomarker for response and survival can be identified. Although a number of publications on predictive markers for response to AZA exist, results are inconsistent and improved response rates did not translate to improved survival. Here, we provide a comprehensive overview comparing the studies published to date.

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Clinical implications of *TP53* mutations in myelodysplastic syndromes treated with hypomethylating agents

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ABSTRACT

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REVIEW ARTICLE

Role Of TP53 mutations in predicting the clinical efficacy of hypomethylating therapy in patients with myelodysplastic syndrome and related neoplasms: a systematic review and meta-analysis

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6.2020

(HMAs) are now a major treatment option for myelodysplastic syndrome (MDS) and related
tients still do not respond and realize poor outcomes. Mutational predictors of treatment efficacy
n. Whether TP53 mutations can be used as predictors of HMA effectiveness has caused heated
ormed a meta-analysis to investigate the predictive value of TP53 mutations to outcomes of HMA
IDS and related neoplasms. We systematically searched PubMed, Embase, the Cochrane Library,
es (published deadline: September 12, 2019). The primary endpoints were overall response rate
al (OS). Odds ratio (OR), hazard ratio (HR), and 95% confidence intervals (CI) were pooled to
etween TP53 mutations and the clinical efficacy of HMAs. Four hundred fifteen papers were
e included in this meta-analysis (N = 2020 participants). The results showed that the presence of
n increased overall response rate with HMA treatment in the subsets that restricted patients in de
HO (World Health Organization) criteria, or NGS (next-generation sequence) group (*P* = 0.005,
pectively). However, TP53 mutations remained poor factors for OS (*P* < 0.00001). Collectively,
utations can predict better ORR when setting more refined subgroups, but TP53 mutations still
oor survival in hypomethylating therapy.

re urgently needed.

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WILEY AJH

RESEARCH ARTICLE

Mutations and karyotype predict treatment response in myelodysplastic syndromes

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Abstract

We examined the influence of mutations and karyotype on conventional treatment response, specifically hematological improvement in anemia, in primary myelodysplastic syndromes (MDS). Cytogenetic and next generation sequencing (NGS)-derived mutation information was available in 357 patients (median age 74 years; 70% males); the revised international prognostic scoring system risk distribution was very high in 11%, high-15%, intermediate 17%, low 40% and very low 16%. At least one mutation was detected in 81% of patients; most frequent were *SF3B1* (32%), *ASXL1* (27%), *TET2* (24%) and *U2AF1* (15%). At median follow-up of 24 months, treatment with hypomethylating agents (HMAs) was documented in 121 (34%) patients, lenalidomide (LEN) in 55 (15%), and erythropoiesis stimulating agents (ESAs) in 136 (38%). *ASXL1* mutations adversely affected response to HMAs (27% vs 48%; *P* = 0.02) and LEN (9% vs 43%; *P* = 0.04), but not ESAs (*P* = 0.6). LEN response was also adversely affected by *U2AF1* mutations (0% vs 42%; *P* = 0.02) and high risk karyotype (0% vs 41% in intermediate vs 47% in low risk; *P* = 0.01). Patients with *SF3B1* mutations were more likely to respond to LEN (56% vs 27%; *P* = 0.04). Contrary to previous reports, we found no association between *TET2* mutations and HMA treatment response (40% vs 41%; *P* = 0.9), even in the absence of *ASXL1* mutations (*P* = 0.4).We conclude that *ASXL1* mutations in MDS predict inferior response to treatment with both HMAs and LEN; response to LEN was also compromised by *U2AF1* mutations and high risk karyotype; *SF3B1* mutations identified patients likely to respond to LEN.

Table 2

Cytogenetic and molecular factors found to affect prognosis and response to hypomethylating agents in patients with MDS.

Factor	Effect on prognosis	Effect on treatment response
Cytogenetic abnormalities		
Monosomal karyotype (MK)	correlated with low OS [37], especially in patients without complex karyotype [38] Addition of MK improves IPSS-R stratification [39]	
Chromosome 7 abnormalities		5-azacytidine better than BSC, especially with complex karyotype [40] Worse response to 5-azacytidine [41]
Chromosome 17 abnormalities	Found mainly in the context of CK and carry its poor prognosis [42]	
Chromosome 3 abnormalities		Lower response rate to 5-azacytidine [43]
Translocations	Rare but correlated with lower OS [44]	Impressive impact of 5-azacytidine on survival of translocation carriers [44]
Molecular factors		
UCK1		Low expression levels correlated with response to 5-azacytidine [48]
TET2 mutations		Better response to treatment [49,50,51] Not predictive of response [52,55,57]
DNMT3A mutations		Independent predictor of response [51]
STAT3/5 signaling profiles		Correlated with response to 5-azacytidine [52]
PARP1	mRNA levels correlated with higher survival rate in patients treated with 5-azacytidine [53]	mRNA levels correlated with better response to 5-azacytidine [54]
ASXL mutations		Adversely correlated with response to 5-azacytidine [55]
TP53 mutations	Correlated with shorter OS [57]	Correlated with high response rates to 5-azacytidine [56] Not correlated with response to 5-azacytidine [57]
Methylation level	High number of methylated genes correlated with shorter OS [58]	High methylation status of RRM1 correlated with response to 5-azacytidine [59]
IDO-1	IDO-1 positivity correlated with shorter OS in patients treated with 5-azacytidine [60]	IDO-1 positivity correlated with 5-azacytidine failure [60]
GATA1, GAT2, FLI1	High GATA2 expression correlated to adverse prognosis in patients treated with 5-azacytidine [61]	GATA1 and FLI1 mRNA expression predict response to 5-azacytidine [61]
sncRNAs		Some expression patterns predict response to 5-azacytidin [62]

MK, monosomal karyotype; IPSS-R, revised international prognostic scoring system; BSC, best supportive care; CK, complex karyotype; UCK1, uridine-cytidine kinase-1; TET2, ten-eleven translocation 2; STAT, signal transducer and activator of transcription; PARP1, poly (ADP-ribose) polymerase 1; RRM1, rivonucleotide reductase subunit 1.

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Overexpression of CXCL7 and CXCL4

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Research Paper

Somatic mutations predict outcomes of hypomethylating therapy in patients with myelodysplastic syndrome

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Keywords: *myelodysplastic syndrome, hypomethylating therapy, mutation, targeted sequencing*

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Table 3: Prognostic factors for overall and AML-free survival

	Variable	Univariate*	Multivariate§	
		P	*P*	HR (95% CI)
Overall survival	Clinical variables			
	Sex (Female vs. Male)	0.006	0.002	3.70 (1.63-8.36)
	IPSS-R (VL/L/Int vs. H/VH)	0.039	0.026	2.36 (1.11-5.02)
	Age (<60 vs. ≥60 years)	0.004	0.073	1.80 (0.95-3.44)
	Gene mutations			
	DNMT1 (WT vs. MT)	0.012	0.031	4.08 (1.14-14.62)
	DNMT3A (WT vs. MT)	0.001	0.006	4.12 (1.51-11.22)
	RAS (WT vs. MT)	<0.001	0.043	2.76 (1.03-7.37)
	TP53 (WT vs. MT)	0.003	0.008	3.17 (1.35-7.43)
AML-free survival	Clinical variables			
	Sex (Female vs. Male)	0.069	0.024	2.85 (1.15-7.09)
	IPSS-R (VL/L/Int vs. H/VH)	0.044	0.005	6.30 (1.77-22.52)
	Gene mutation			
	DNMT3A (WT vs. MT)	<0.001	<0.001	12.81 (4.04-40.63)
	TP53 (WT vs. MT)	0.074	0.047	2.80 (1.01-7.75)
	RAS (WT vs. MT)	<0.001	0.001	7.04 (2.24-22.12)

* Univariate survival analysis was performed using the Kaplan-Meier method.
§ Cox proportional hazards model was built with the variables with $P<0.1$ in univariate analysis.
IPSS-R, revised International Prognostic Scoring System; VL, very low; L, low; Int, intermediate; H, high; VH, Very High; WT, wild type; MT, mutant type

- Score 1: male-gender, IPSS-R H/VH, and each mutation of *DNMT1*, *DNMT3A*, *RAS*, and *TP53*
- Score 0: female-gender, IPSS-R VL/L/Int, wild-type of the fougenes.
- Four groups: low (score sum=0), intermediate-1 (score sum=1), intermediate-2 (score sum=2) and high (score sum ≥3) risk group.
- As the sum of the scores increased, OS ($P<0.001$) and AFS ($P<0.001$) decreased in a score dependent manner (Figure 4).

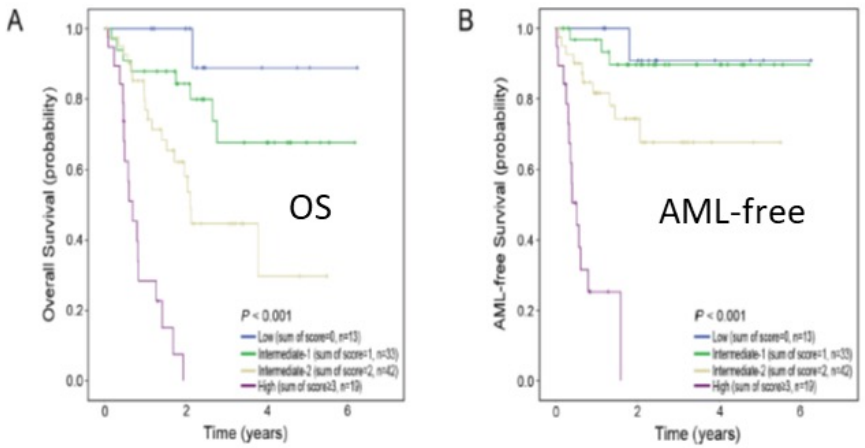

Figure 4: Risk scoring system for predicting survival. Kaplan–Meier estimates of overall survival **A.** and AML-free survival **B.** for four risk groups. As sum of scores increased, overall survival and AML-free survival decreased in a score-dependent manner.

Leukemia (2014) 28, 78–87

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ORIGINAL ARTICLE

Impact of molecular mutations on treatment response to DNMT inhibitors in myelodysplasia and related neoplasms

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We hypothesized that specific molecular mutations are important biomarkers for response to DNA methyltransferase inhibitors (DNMT inhibitors) and may have prognostic value in patients with myelodysplastic syndromes (MDS). Mutational analysis was performed in 92 patients with MDS and related disorders who received 5-azacytidine ($n=55$), decitabine ($n=26$) or both ($n=11$). Mutational status was correlated with overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) by univariate and multivariate analysis. Risk stratification models were created. *TET2*, *DNMT3A*, *IDH1/IDH2*, *ASXL1*, *CBL*, *RAS* and *SF3B1* mutations were found in 18, 9, 8, 26, 3, 2 and 13% of patients, respectively. In multivariate analysis, $TET2^{MUT}$ and/or $DNMT3A^{MUT}$ ($P=0.03$), platelets $\geq 100\times10^9$/l ($P=0.007$) and WBC $<3.0\times10^9$/l ($P=0.03$) were independent predictors of better response. $TET2^{MUT}$ and/or $DNMT3A^{MUT}$ ($P=0.04$) status was also independently prognostic for improved PFS, as were good or intermediate cytogenetic risk ($P<0.0001$), age <60 ($P=0.0001$), treatment with both 5-azacytidine and decitabine ($P=0.02$) and hemoglobin ≥ 10 g/dl ($P=0.01$). Better OS was associated with $ASXL1^{WT}$ ($P=0.008$) and $SF3B1^{MUT}$ ($P=0.01$), and, similar to PFS, cytogenetic risk ($P=0.0002$), age ($P=0.02$) and hemoglobin ($P=0.04$). These data support the role of molecular mutations as predictive biomarkers for response and survival in MDS patients treated with DNMT inhibitors.

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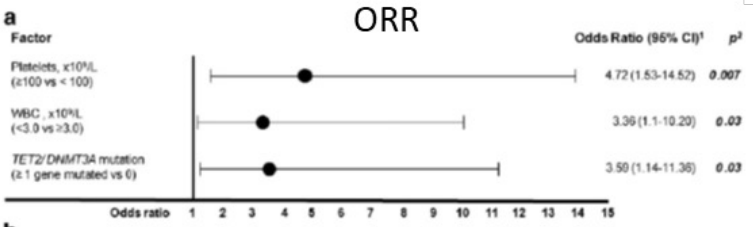
Keywords: DNMT inhibitors; molecular mutations; prognostic factors

ORR

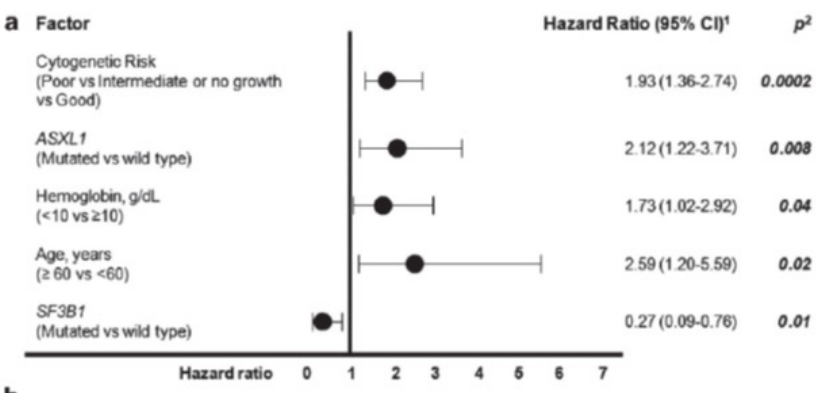


b

Feature	Category	Score
Platelets, x10⁹/L	≥100 < 100	0 1
WBC , x10⁹/L	<3.0 ≥3.0	0 1
TET2/DNMT3A mutation	One or both genes mutated Both genes wild type	0 1

Total Score	Risk Group	N (%)	N (%) Response	p²
0 or 1	Favorable	23 (26%)	10 (43%)	
2	Intermediate	52 (57%)	12 (23%)	
3	Unfavorable	16 (18%)	-0-	0.002

OS



b

Feature	Category	Score
Cytogenetic Risk	Good Intermediate or no growth Poor	0 2 5
ASXL1	Wild type Mutated	0 3
Hemoglobin, g/dL	≥10 <10	0 2
Age	< 60 ≥ 60	0 4
SF3B1	Mutated Wild type	0 8

Total Score	Risk Group	N (%)	Median Survival (months)	p²
<12	Favorable	49 (53%)	30.7	
≥12	Unfavorable	43 (47%)	7.9	<0.0001

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Research Paper

Impact of the number of mutations in survival and response outcomes to hypomethylating agents in patients with myelodysplastic syndromes or myelodysplastic/myeloproliferative neoplasms

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Keywords: *myelodysplastic syndromes; chronic myelomonocytic leukemia; response; prognosis; mutations*

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ABSTRACT

The prognostic and predictive value of sequencing analysis in myelodysplastic

Table 3: New model incorporating IPSS-R and mutation variables

Score	N	Events	Category	Median OS (months)
0	26	5	Low	NR
0.5	22	7		
1	10	4	Int	29
1.5	33	16		
2	1	0		
2.5	20	17	High	12
3.5	2	2		

Low = Category Low of the new Molecular IPSS-R model based on OS of patients with scores 0–0.5. Int = Category Intermediate of the new Molecular IPSS-R model based on OS of patients with scores 1–2. High = Category High of the new Molecular IPSS-R model based on OS of patients with scores 2.5–3.5.

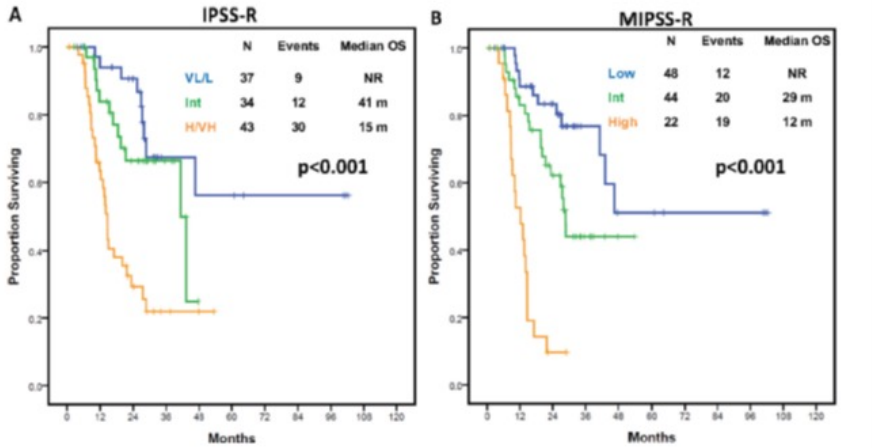

Figure 4: Overall survival outcomes by IPSS-R and molecular IPSS-R model in the discovery cohort. (A) Kaplan-Meier estimates of overall survival in the study cohort according to the integrated Molecular IPSS-R model. (B) Kaplan-Meier estimates of overall survival in the study cohort by IPSS-R scoring system.

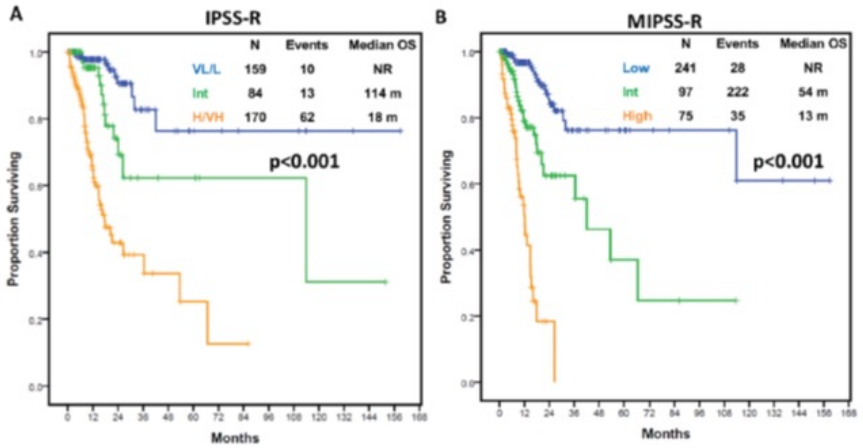

Figure 5: Overall survival outcomes by IPSS-R and molecular IPSS-R model in the additional cohort. (A) Kaplan-Meier estimates of overall survival in the additional cohort according to the integrated Molecular IPSS-R model. (B) Kaplan-Meier estimates of overall survival in the additional cohort by IPSS-R scoring system.

Computational modeling and digital simulation platform for assessing genomics as predictor of treatment response in individual patients

REGULAR ARTICLE

blood advances

A genomics-informed computational biology platform prospectively predicts treatment responses in AML and MDS patients

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Key Points

- We describe a comprehensive computational biology modeling and digital drug simulation platform.
- Somatic gene mutations and gene copy number variations found in individual patients were used for predictions of treatment responses.

Patients with myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) are generally older and have more comorbidities. Therefore, identifying personalized treatment options for each patient early and accurately is essential. To address this, we developed a computational biology modeling (CBM) and digital drug simulation platform that relies on somatic gene mutations and gene CNVs found in malignant cells of individual patients. Drug treatment simulations based on unique patient-specific disease networks were used to generate treatment predictions. To evaluate the accuracy of the genomics-informed computational platform, we conducted a pilot prospective clinical study (NCT02435550) enrolling confirmed MDS and AML patients. Blinded to the empirically prescribed treatment regimen for each patient, genomic data from 50 evaluable patients were analyzed by CBM to predict patient-specific treatment responses. CBM accurately predicted treatment responses in 55 of 61 (90%) simulations, with 33 of 61 true positives, 22 of 61 true negatives, 3 of 61 false positives, and 3 of 61 false negatives, resulting in a sensitivity of 94%, a specificity of 88%, and an accuracy of 90%. Laboratory validation further confirmed the accuracy of CBM-predicted activated protein networks in 17 of 19 (89%) samples from 11 patients. Somatic mutations in the *TET2*, *IDH1/2*, *ASXL1*, and *EZH2* genes were discovered to be highly informative of MDS response to hypomethylating agents. In sum, analyses of patient cancer genomics using the CBM platform can be used to predict precision treatment responses in MDS and AML patients.

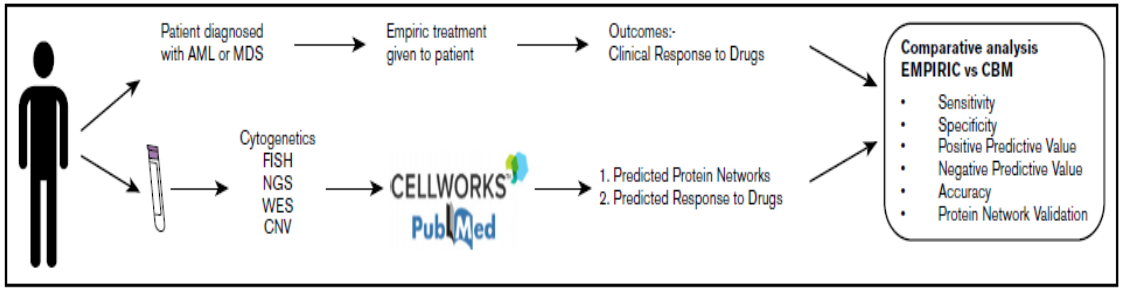


Figure 1. Study schema of the iCare 1 clinical study. NGS, next-generation sequencing; WES, whole-exome sequencing.

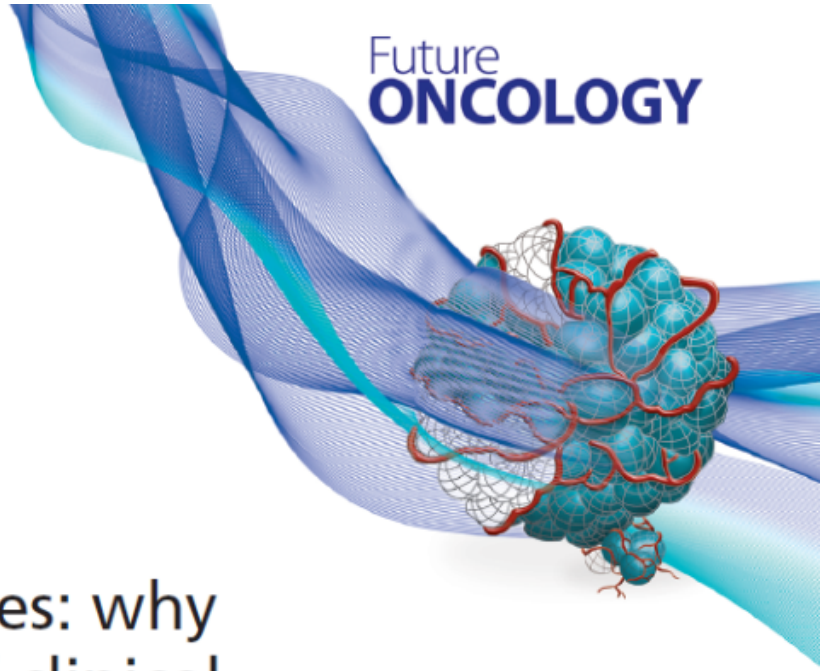
Physician Choice Drug	N[a]	Correct prediction	Positive response prediction		Negative response prediction	
			T	F	T	F
HMA [b]	18	16/18	4		12	2
Lenalidomide	2	2/2			2	
Ruxolitinib	2	2/2	2			
Imatinib	1	1/1	1			
HiDAC [c]	17	17/17	14		3	
Bortezomib	1	1/1			1	
Cytarabine + fludarabine	1	1/1			1	
Vorasidenib (AG-881)	1	1/1			1	
7+3	18	14/18	12	3	2	1
Overall	61	55/61	33	3	22	3

[a] Number of patients for whom CBM-based predictions for any given drug were generated. Each patient could have more than 1 drug prediction.
[b] Azacitidine or decitabine.
[c] 2-3 g/m^2.
P values < .05 were statistically significant

	Physician		
Cellworks	Responder	Nonresponder	Total
Responder	33	3	36
Nonresponder	3	22	25
Total	36	25	61

	Estimate	Lower 95% CI	Upper 95% CI
Control (Physician)	59.0%	45.7%	71.4%
Concordance	90.2%	79.8%	96.3%
Sensitivity	91.7%	77.5%	98.2%
Specificity	88.0%	68.8%	97.5%
PPV	91.7%	77.5%	98.2%
NPV	88.0%	68.8%	97.5%
P value	6.42E-05		

Figure 4. Prediction values of CBM predictions compared with actual clinical outcomes in terms of actual clinical improvement (TP response) and no clinical improvement (TN response). The 95% confidence interval (CI) was calculated using the Clopper-Pearson test.



Review

Real-world use and outcomes of hypomethylating agent therapy in higher-risk myelodysplastic syndromes: why are we not achieving the promise of clinical trials?

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Table 1. Hypomethylating agent use and persistence.

Author (year)	Data source	Population	HMA use (%)	Definition of nonpersistence	Proportion of patients who were nonpersistent (%)	Ref.
Bell *et al.* (2019)	Optum database, 2008–2015	Patients diagnosed with higher-risk MDS, n = 335	MDS-related therapy received by 62.4% of patients; 89.5% of patients receiving MDS-related first-line therapy received HMAs	NR	NR	[25]
Cheng *et al.* (2021)	IBM MarketScan Commercial Claims and Encounters database and the Medicare Supplemental and Coordination of Benefits database, 2011–2018	Diagnosed with MDS and starting HMA therapy, n = 2400	NA (treated population)	Gap of ≥60 days before the end of the landmark period	4-month landmark period, 18.8% 9-month landmark period, 43.7%	[36]
Cogle *et al.* (2017)	Optum Clinformatics Data Mart, 2009–2011	Incident cases with MDS, n = 4151	Initiating HMA therapy: 2.3% in year 1 2.7% in year 2 2.9% in year 3	NR	NR	[30]
Corman *et al.* (2021)	SEER-Medicare database, January 2011–December 2015	Diagnosed with RAEB, n = 1190	56.0% (ever prescribed)	Less than four cycles or a gap of ≥90 days between consecutive cycles	44.6%	[19]
Davidoff *et al.* (2020)	SEER-Medicare database, 2001–2004 and 2006–2011	Diagnosed with RAEB 2001–2004, n = 581; 2006–2011, n = 1295	2001–2004, 3.6% 2006–2011, 43.0%	NR	NR	[18]
Demakos *et al.* (2014) (abstract)	Claims, database not specified, 2009–2011	Newly diagnosed with MDS	13.1%	Less than six cycles	69.1%	[26]
Ma *et al.* (2018)	GE Centricity Electronic Medical Record database, 2006–2014	Patients with MDS, n = 5162 Patients who received ≥1 erythropoiesis-stimulating agent, iron chelation therapy, lenalidomide or HMA, n = 2079	Among patients receiving ≥1 therapy, 12.1% received HMA first-line, 6.2% received HMA second- or third-line	NR	NR	[29]
Mukherjee *et al.* (2014)	US commercial claims database, 2009–2012	Patients who received HMA, n = 1366	NA (treated population)	Less than five cycles azacitidine Less than five cycles decitabine	48.0% 52.0%	[35]
Sekeres *et al.* (2008)	Surveys of US hematologists and medical oncologists, June 2005–January 2007, n = 101	Patients with MDS seen by participants: recently diagnosed, n = 670; established patients, n = 3844	Newly diagnosed vs established patients: azacitidine, 16 vs 11–15%; decitabine, 2 vs 0–4%	NR	NR	[27]
Steensma *et al.* (2014)	Survey	Patients with MDS, n = 477; physicians managing MDS, n = 120	35% of patients	Less than six cycles azacitidine Less than four cycles decitabine	41% 33%	[28]
Stein *et al.* (2019)	SEER-Medicare database, 2006–2017	Diagnosed with MDS 2009–2017 and treated with HMAs, n = 3046	NA (treated population)	Less than four cycles	45.3%	[20]
Zeidan *et al.* (2020)	SEER-Medicare database	Diagnosed 2004–2013 and received HMA therapy, n = 2086	NA (treated population)	Less than four cycles Less than six cycles	42.7% 60.6%	[22]

AML: Acute myeloid leukemia; HMA: Hypomethylating agent; MDS: Myelodysplastic syndrome; NA: Not applicable; NR: Not reported; RAEB: Refractory anemia with excess blasts; SEER: Surveillance, epidemiology and end results program.

Table 2. Clinical outcomes according to persistence.

Author (year)	Data source	Population	Definition of persistence/ nonpersistence	Clinical outcomes, nonpersistent vs persistent	Ref.
Cabrero *et al.* (2015)	Clinical trials of HMA	Patients who stopped therapy while in response, n = 16	<12 vs 12 cycles	1-year PFS: 17 vs 50%, p = 0.062 Median OS: 4 vs 20 months, p = 0.043	[39]
Cheng *et al.* (2021)	IBM MarketScan Commercial Claims and Encounters database and the Medicare Supplemental and Coordination of Benefits database from 2011 to 2018	Diagnosed with MDS and starting HMA therapy, n = 2400	Nonpersistence, gap of ≥60 days in treatment before end of landmark period	Mean time to AML transformation, 22.0 vs 38.5 months Incidence rate of AML during follow-up from HMA initiation, adjusted HR: 1.88; 95% CI: 1.53–2.32; p < 0.001	[36]
Corman *et al.* (2021)	SEER-Medicare database	Diagnosed with RAEB between January 2011 and December 2015, n = 1190	Less than four cycles or a gap of ≥90 days between consecutive cycles	Median OS, 9.5 vs 13.8 months (No HMA therapy, 3.8 months)	[19]
Zeidan *et al.* (2020)	SEER-Medicare database	Diagnosed 2004–2013 and received HMA therapy, n = 2086	Less than four vs ≥4 cycles	Median OS, 4 vs 16 months; p < 0.01	[22]

AML: Acute myeloid leukemia; HMA: Hypomethylating agent; HR: Hazard ratio; MDS: Myelodysplastic syndrome; OS: Overall survival; PFS: Progression-free survival; RAEB: Refractory anemia with excess blasts; SEER: Surveillance, epidemiology and end results program.

Table 3. Economic impact of early discontinuation.

Author (year)	Data source	Population	Definition of persistence/ nonpersistence	Economic outcomes	Ref.
Cheng *et al.* (2021)	IBM MarketScan Commercial Claims and Encounters database and the Medicare Supplemental and Coordination of Benefits database, 2011–2018	Patients with MDS starting HMA therapy, n = 2400	≥60-day gap in treatment before the end of 4-month landmark period	Nonpersistent vs persistent: Significantly higher all-cause HRU for: ER visits (IRR: 1.16; 95% CI: 1.01–1.34), inpatient visits (IRR: 1.46; 95% CI: 1.28–1.67); and inpatient days (IRR: 1.40; 95% CI: 1.33–1.46); all $p < 0.001$ Significantly higher non-HMA-related HRU burden for: ER visits (IRR: 1.30; 95% CI: 1.12–1.50), inpatient visits (IRR: 1.48; 95% CI: 1.30–1.69), inpatient days (IRR: 1.41; 95% CI: 1.36–1.46) and outpatient visits (IRR: 1.12; 95% CI: 1.10–1.14); all $p < 0.001$ Fewer HMA-related outpatient visits (IRR: 0.09; 95% CI: 0.09–0.10) and marginally fewer any-cause outpatient visits (IRR: 0.82; 95% CI: 0.80–0.83); all $p < 0.001$	[36]
Cogle *et al.* (2017)	Optum Clinformatics Data Mart, 2008–2009	Patients with refractory MDS following HMA therapy, n = 402	Stopped HMA therapy	Total healthcare costs following HMA failure: US$76,945 (SD US$92,764) during the first 6 months (n = 402); US$50,732 (SD US$77,885) for months 19–24 (n = 95)	[30]
Joshi *et al.* (2021)	SEER-Medicare database, 2011–2016	Patients diagnosed with RAEB and who received HMAs, n = 664	Less than four cycles or a gap of ≥90 days between cycles	Nonpersistent vs persistent: Significantly higher hospitalizations (IRR: 1.54; $p = 0.001$), ER visits (IRR: 1.32; $p < 0.001$), skilled nursing facility use (IRR: 2.16; $p = 0.003$), home health visits (IRR: 1.34; $p = 0.024$) and hospice care use (IRR: 2.56; $p < 0.001$). Significantly lower frequency of outpatient (IRR: 0.87; $p = 0.026$) and physician visits (IRR: 1.23; $p < 0.001$) Significantly ($p < 0.05$) higher total PPPM costs (US$18,039 vs US$13,893), particularly for hospitalizations (US$3375 vs US$2131), and ER costs (US$5517 vs US$2867)	[47]
Stein *et al.* (2021)	SEER-Medicare database, 2006–2016	Patients diagnosed with MDS and initiated on HMA therapy, n = 3046	Treatment success, defined as receipt of ≥7 cycles, SCT or RBC transfusion independence Treatment failure, defined as disease progression, HMA discontinuation, resumption of RBC transfusion dependence, AML or death	Treatment success vs treatment failure (pre-HMA) vs treatment failure (post-HMA), per 100 patients per month: Inpatient admissions, 7.5 vs 20.4 vs 35.3 Total healthcare costs: US$8069 vs US$13,809 vs US$19,242 Outpatient costs: US$7028 vs US$9099 vs US$3702 Inpatient costs: US$1002 vs US$4616 vs US$15,451	[48]

AML: Acute myeloid leukemia; ER: Emergency room; HMA: Hypomethylating agent; HRU: Healthcare resource use; IRR: Incidence rate ratio; MDS: Myelodysplastic syndrome; PPPM: Per patient per month; RAEB: Refractory anemia with excess blasts; RBC: Red blood cell; SCT: Stem cell transplant; SEER: Surveillance, epidemiology and end results program.

Real-world utilization & persistence of hypomethylating agent therapy for higher-risk myelodysplastic syndromes

- Data from real-world studies suggest that around half of patients with higher-risk myelodysplastic syndromes (MDS) do not receive hypomethylating agent (HMA) therapy.
- In addition to underutilization, real-world studies report low rates of persistence with HMA therapy.
- Patients generally require at least four to six cycles in order to achieve responses to HMA therapy, and further improvements in outcomes may be achieved beyond this time point; however, studies have reported that around 33–45% of patients received less than four cycles of therapy, and that 41–69% received less than five or six cycles.

Impact of persistence with HMA therapy on clinical outcomes

- In real-world studies, nonpersistence with HMA therapy has been associated with more rapid disease progression, shorter overall survival and higher risk of progression from MDS to acute myeloid leukemia.

Factors influencing persistence with HMA therapy

- Early discontinuation of HMA therapy can occur for reasons that may be considered clinically driven (e.g., toxicity or disease progression) or nonclinically driven (e.g., factors relating to the logistics of therapy administration, or provider inexperience).
- Alongside clinical factors, addressing nonclinical reasons for discontinuation could further improve real-world outcomes, and therefore should also be a key consideration for clinicians and healthcare decision-makers.

Economic consequences of nonpersistence with HMA therapy

- Persistence with HMA therapy among patients with MDS has also been found to have an economic impact, with nonpersistence associated with higher healthcare resource utilization and costs.

Improving real-world clinical & economic outcomes with HMA therapy

- The data reviewed indicate the need to understand the drivers of underutilization and poor persistence with HMA therapy, and for approaches to improve utilization and persistence in real-world clinical practice to ensure patients achieve the optimum benefit from HMA therapy.
- Potential approaches include the use of oral HMA therapies, and improving clinician, patient and caregiver understanding of the need for prolonged use of HMA therapy.

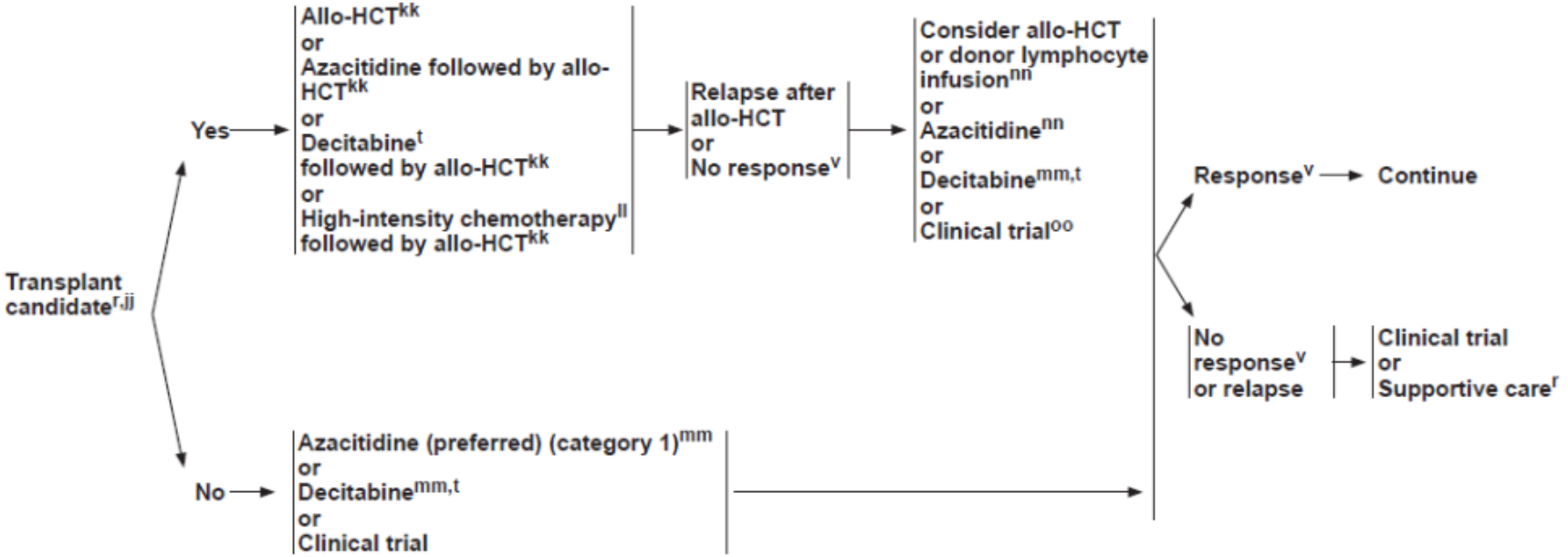
National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2021
Myelodysplastic Syndromes

NCCN Guidelines Index
Table of Contents
Discussion

PROGNOSTIC CATEGORY[o] | **TREATMENT**

IPSS-R: Intermediate,[p] High, Very High
IPSS: Intermediate-2, High
WPSS: High, Very High



bjh guidelines

British Society for Haematology guidelines for the management of adult myelodysplastic syndromes

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Recommendations

High-risk patients NOT eligible for allogeneic transplant:

- Patients requiring treatment should be considered for any appropriate clinical trial.
- In fit older patients lacking an adverse karyotype, the options of therapy with a hypomethylating agent *versus* intensive chemotherapy should be carefully discussed. Where intensive chemotherapy outside a clinical trial is planned, standard AML induction regimens should be used (2B).
- Azacitidine is the preferred hypomethylating agent and is recommended as first-line therapy for patients ineligible for stem cell transplant with IPSS Intermediate-2 and high-risk MDS (IPSS-R Intermediate (score >3·5)/ high/very high-risk groups) or AML with 20–30% blasts. Grade 1A (on the basis of a single randomised control trial).
- The recommended dose of azacitidine is 75 mg/m^2 daily for seven consecutive days but a 5–2–2 schedule (with a two-days weekend gap) is acceptable where it is not practical to offer seven consecutive days and outcomes with the two schedules appear comparable (2B).
- Outcomes of patients treated with azacitidine in routine clinical practice show a considerably shorter OS than the pivotal clinical trial (12·4–18·9 months compared to 24·5 months). Patients should be made aware of this.
- Responding patients should continue azacitidine while their response is maintained (1A).
- The decision to stop or continue azacitidine in patients who fail to achieve any response after six cycles, but who have stable disease, is dependent upon clinician and patient preference (2B).
- Patients failing therapy with hypomethylating agents should be considered for any appropriate clinical trial.

Recommendations

Allogeneic transplant in MDS.

- All transplant-eligible MDS patients should be discussed with a transplant physician at a MDT both at diagnosis and at disease progression (2B).
- Additional prognostic factors such as transfusion burden, depth of cytopenias, cytogenetics and BM fibrosis should be assessed when considering the optimal timing of transplant for lower-risk MDS patients (2B).
- Higher-risk MDS patients with >10% blasts may be considered for cytoreductive therapy or hypomethylating agents prior to transplant (2B).
- Up-front transplant may be considered in patients with 5–10% blasts with slowly progressive disease or in those with a hypocellular or fibrotic BM (2B).
- Transplant is not routinely recommended for patients with *TP53* mutation in association with a complex monosomal karyotype due to poor outcomes (2B).
- Eligibility for transplant should be guided by HCT-CI and EBMT risk score (2B).
- Performance status and age should be used to inform choice of myeloablative or reduced-intensity conditioning (2B).

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rapid communications

Comparison Between 5-Azacytidine Treatment and Allogeneic Stem-Cell Transplantation in Elderly Patients With Advanced MDS According to Donor Availability (VidazaAllo Study)

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abstract

PURPOSE In contrast to 5-azacytidine (5-aza), allogeneic stem-cell transplantation (HSCT) represents a curative treatment strategy for patients with myelodysplastic syndromes (MDS), but therapy-related mortality (TRM) limits its broader use in elderly patients with MDS. The present prospective multicenter study compared HSCT following 5-aza pretreatment with continuous 5-aza treatment in patients with higher-risk MDS age 55-70 years.

METHODS One hundred ninety patients with a median age of 63 years were enrolled. Patients received 4-6 cycles of 5-aza followed by HLA-compatible HSCT after reduced-intensity conditioning or by continuous 5-aza if no donor was identified.

RESULTS Twenty-eight patients did not fulfill inclusion criteria (n = 20), died (n = 2) withdrew informed consent (n = 5), or were excluded for an unknown reason (n = 1). 5-aza induction started in 162 patients, but only 108 (67%) were eligible for subsequent allocation to HSCT (n = 81) or continuation of 5-aza (n = 27) because of disease progression (n = 26), death (n = 12), or other reasons (n = 16). Seven percent died during 5-aza before treatment allocation. The cumulative incidence of TRM after HSCT at 1 year was 19%. The event-free survival and overall survival after 5-aza pretreatment and treatment allocation at 3 years were 34% (95% CI, 22 to 47) and 50% (95% CI, 39 to 61) after allograft and 0% and 32% (95% CI, 14 to 52) after continuous 5-aza treatment ($P < .0001$ and $P = .12$), respectively. Fourteen patients progressing after continuous 5-aza received a salvage allograft from an alternative donor, and 43% were alive at last follow-up.

CONCLUSION In older patients with MDS, reduced-intensity conditioning HSCT resulted in a significantly improved event-free survival in comparison with continuous 5-aza therapy. Bridging with 5-aza to HSCT before is associated with a considerable rate of dropouts because of progression, mortality, and adverse events.

J Clin Oncol 39:3318-3327.

TABLE 1. Patient Characteristics at Study Entry

Variable	Start of 5-aza Treatment (n = 162)
Median age, years (range)	63 (55-70)
Sex, No.	
Male	100
Female	62
Disease classification, No.	
MDS	125
RAEB 1 or 2	105
AML < 30% blasts (RAEB-T)	30
CMML	7
Median blasts, No. (range)	13 (0-30)
IPSS, No.	
Intermediate-1	6
Intermediate-2	84
High-risk	70
At least intermediate-2	2[a]
ECOG, No.	
0	5
1	73
2	4

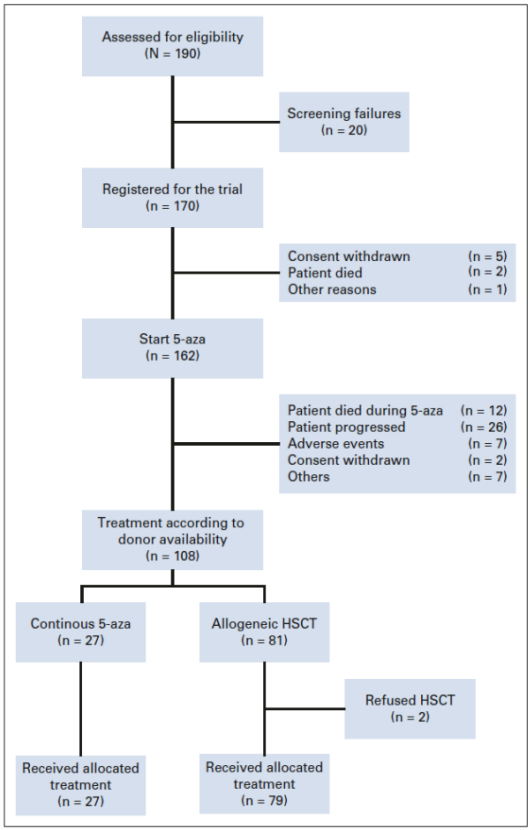


FIG 1. Flow diagram. 5-aza, 5-azacytidine; HSCT, allogeneic stem-cell transplantation.

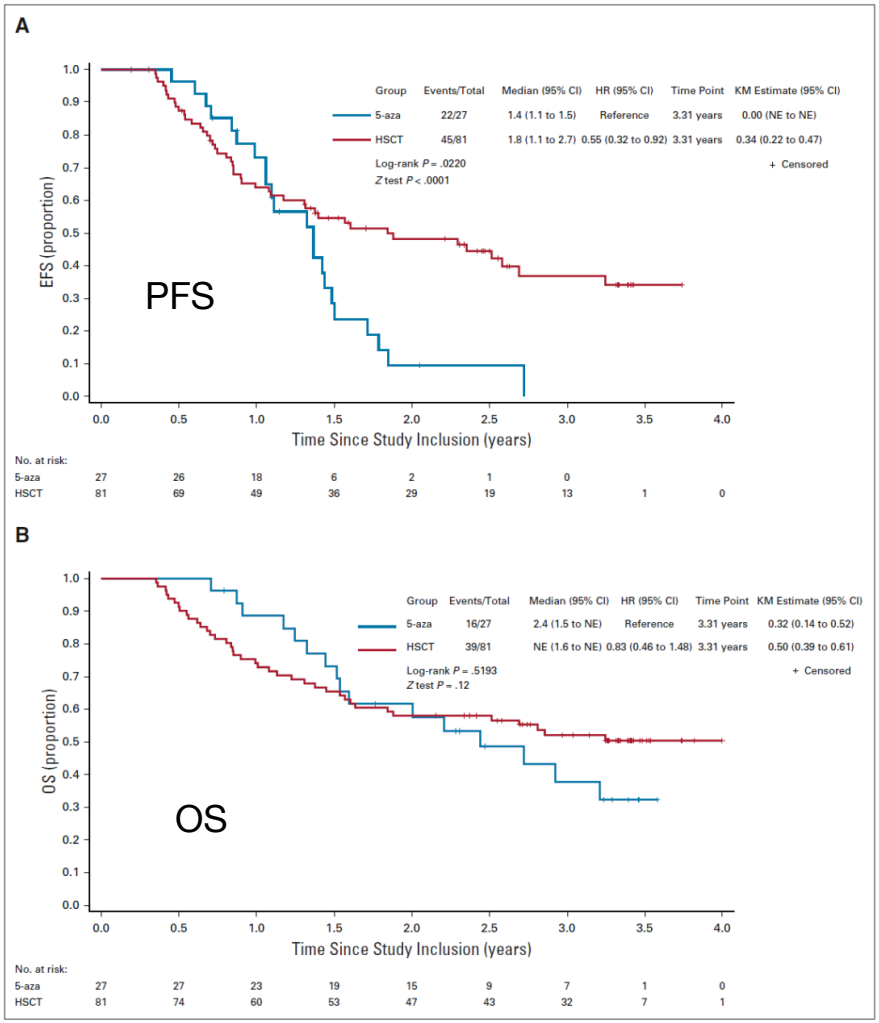


FIG 2. Kaplan-Meier estimates of (A) EFS and (B) OS after allocation to 5-aza or HSCT. 5-aza, 5-azacytidine; EFS, event-free survival; FAS, full analysis data set; HR, hazard ratio; HSCT, allogeneic stem-cell transplantation; KM, Kaplan-Meier; NE, not evaluable; OS, not evaluable, overall survival.

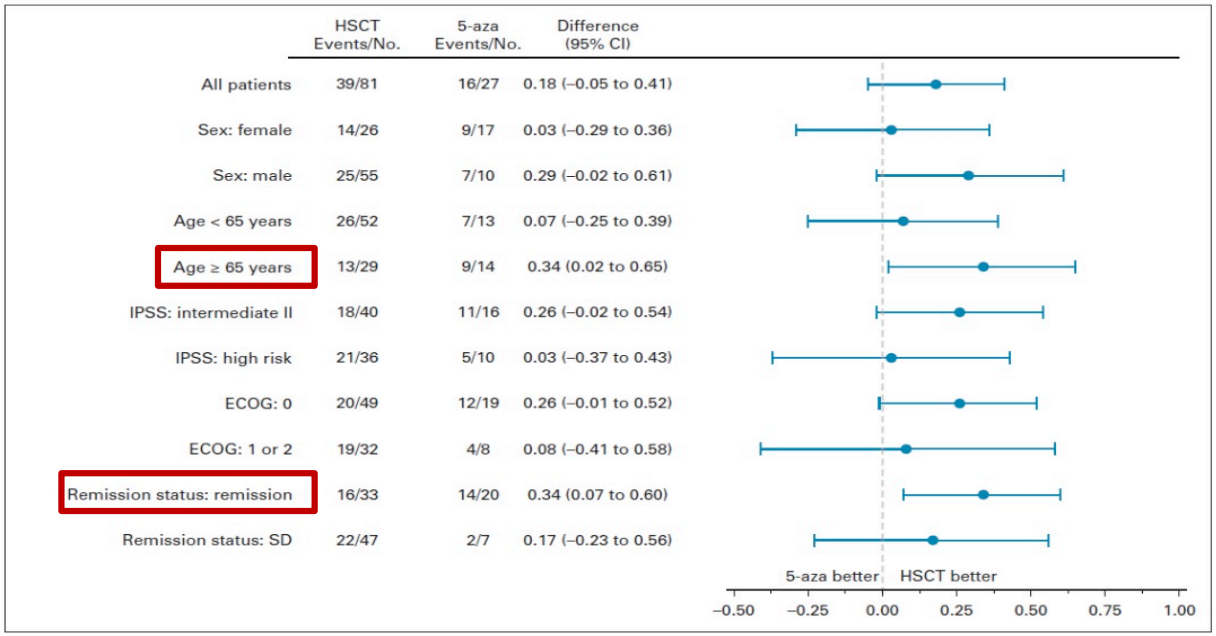


FIG 3. Forest plot as difference in 3-year overall survival by subgroups. 5-aza, 5-azacytidine; ECOG, Eastern Cooperative Oncology Group; HSCT, allogeneic stem-cell transplantation; IPSS, International Prognostic Scoring System; SD, stable disease.

CONTEXT

Key Objective

Can allogeneic stem-cell transplantation (HSCT) in older patients with myelodysplastic syndromes improve overall survival in comparison with standard 5-azacytidine (5-aza) therapy?

Knowledge Generated

A high number of patients progressed or died during 5-aza induction phase. After 2 years, HSCT improves event-free survival but not overall survival in comparison with continuous 5-aza therapy.

Relevance

HSCT should be considered as a reasonable treatment option for older patients with higher-risk myelodysplastic syndromes, and the value of 5-aza bridging before transplantation is questionable.

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

OPTIMIZING HMA THERAPIES THROUGH COMBINATION THERAPIES

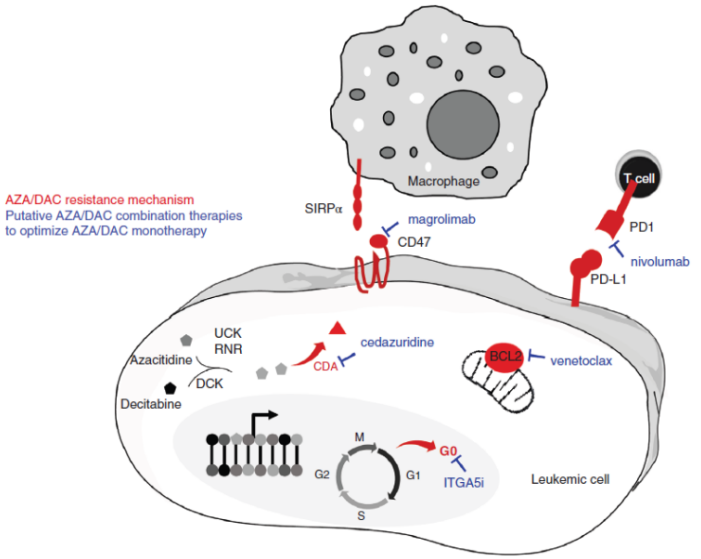
Histone deacytelase inhibitors to reactivate gene expression

All-trans retinoic acid to induce differentiation

Targeting metabolism to increase bioavailability

Combinations with immune checkpoint inhibition

Combinations with drugs that target anti-apoptotic proteins



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Real-world experience with venetoclax and hypomethylating agents in myelodysplastic syndromes with excess blasts

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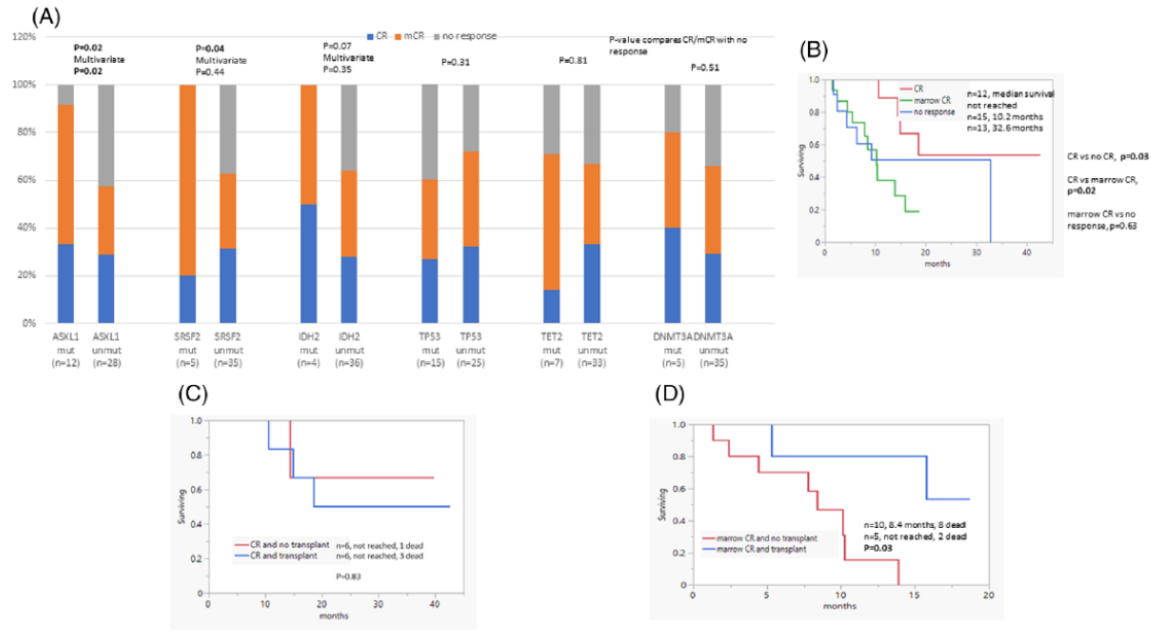

FIGURE 1 (A) Response status based on mutational profile in 40 patients with myelodysplastic syndromes with excess blasts (MDS-EB). (B) Survival of 40 patients with myelodysplastic syndromes with excess blasts (MDS-EB) stratified by response to hypomethylating agent and venetoclax. (C) Survival of 12 patients with myelodysplastic syndromes with excess blasts (MDS-EB) achieving complete remission (CR) following hypomethylating agent and venetoclax stratified by transplant. (D) Survival of 15 patients with myelodysplastic syndromes with excess blasts (MDS-EB) achieving marrow complete remission (mCR) following hypomethylating agent and venetoclax stratified by transplant

Oral hypomethylating agents: beyond convenience in MDS

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Oral hypomethylating agents (HMAs) represent a substantial potential boon for patients with myelodysplastic syndrome (MDS) who have previously required between 5 and 7 visits per month to an infusion clinic to receive therapy. For patients who respond to treatment, ongoing monthly maintenance visits represent a considerable burden to quality of life, and for those who are early in therapy, these sequential visits may tax transportation and financial resources that would be optimally distributed over the treatment cycle to facilitate transfusion support. The availability of oral HMAs may support the optimal application of these agents by contributing to adherence and lessening the burden of therapy, potentially encouraging patients to stay on longer-term treatment. Distinct pharmacokinetic profiles for the recently approved oral HMAs (oral azacitidine and decitabine-cedazuridine) result in differential toxicity profiles and have prompted their clinical trial development in lower- and higher-risk MDS, respectively.

Unmodified oral azacitidine

Other oral HMAs in development

Oral decitabine/cedazuridine

Conclusions

- *Higher-risk MDS carries a major risk of transformation to AML and short survival, particularly in patients who are not eligible for allogeneic transplantation*
- *Key treatment goals should aim to modify this disease course, that appears to be worse in real-life studies than in large pivotal clinical trials including patients treated with HMAs, where a clinical benefit is observed in approximately 40–50% of cases*

- *Currently, no clear biomarker for response and survival can be identified.*
- *Although a number of publications on predictive markers for response to AZA exist, particularly using a combination of clinical and molecular prognostic factors, results are still inconsistent and improved response rates did not translate to improved survival.*

- *There is therefore need to identify new biomarkers to define patients with a high probability of response and prolonged survival*
- *Likewise, there is need to develop novel and effective oral and combination treatments with manageable safety profiles, which do not increase myelosuppression, to improve the current results obtained with HMA monotherapy*