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Characteristics and Clinical Outcomes of *DDX41*-Mutated Myeloid Neoplasms Treated with Lenalidomide: Single-Center Retrospective Study

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BACKGROUND

- *DDX41* is the most commonly mutated gene in myeloid neoplasms (MN) with germline predisposition
- *DDX41* mutations promote leukemogenesis through multiple pathways including R-loop accumulation, pre-mRNA splicing variations, and defective snoRNA processing
- Efficacy of lenalidomide for MDS with del(5q) is well established but use in the context of other genetically-defined subtypes of MNs is less studied
- Available evidence suggests high response rates for lenalidomide in *DDX41* mutated (*DDX41*m) MN although the mechanism remains unclear

METHODS

- This study was a single-center retrospective review of adult patients (≥18 years) with a *DDX41*m MN treated with at least one cycle of lenalidomide at between 2017 and 2024
- Inclusion required pathogenic or likely pathogenic *DDX41* mutation(s) identified on in-house bone marrow next-generation sequencing targeted panel (sensitivity, variant allele frequency (VAF) ~1%). Mutations were classified as either somatic or germline based on VAF, existing population data, and resolution or persistence in remission (if applicable)
- Outcomes of interest included composite complete remission (CRc), defined as CR+CR_h+CR_i for AML and CR+CR_h+CR_L+CR equivalent for MDS, median overall survival (mOS) calculated from time of lenalidomide initiation to death, relapse, or censored at last follow up, and median relapse free survival (mRFS) calculated from time of best response with lenalidomide to death, relapse, or censored at last follow up. mRFS was not censored for hematopoietic stem cell transplant (HSCT).

RESULTS

- 10 patients with *DDX41*m MN were identified
  - 5 MDS (50%), 5 AML (50%)
- **No patients with concurrent del(5q) at the time of lenalidomide therapy**
- Most patients received lenalidomide for **R/R disease** (n=7); two patients received it in the first-line setting, and one as maintenance therapy in CR1
- Most common dosing regimen was **10 mg daily for 21-days of a 28-day cycle** (n=9)
- Lenalidomide given as monotherapy in 8 patients (80%) and in combination with HMA in 2 patients (20%)
- Median of 13.5 cycles of lenalidomide

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TABLE 1. CHARACTERISTICS AT TIME OF LENALIDOMIDE THERAPY

Variable n (%) or Median [range]		Overall *DDX41*m MN n=10	Newly Diagnosed n=3	Relapsed/Refractory n=7
Diagnosis	MDS AML	5 (50%) 5 (50%)	2 (67%) 1 (33%)	3 (43%) 4 (57%)
Mutation(s)	Germline + Somatic Germline-only Somatic-only	7 (70%) 1 (10%) 2 (20%)	2 (67%) 1 (33%) 0	5 (71%) 0 2 (29%)
DDX41 VAF	Germline Somatic	51% [28-57%] 6% [2-16%]	10% (5-14%)	50% [28-53%] 10% [2-16%]
Age (years)		74 [61-81]	56% [49-57%]	76 [61-81]
WBC (K/uL)		1.7 [0.9-5.2]	2.4 [1.5-5.2]	1.6 (0.9-2.7)
Hemoglobin (g/dL)		10.5 [7.8-10.8]	10.5 [10.1-10.8]	9.3 (7.8-10.8)
Platelet count (K/uL)		58 [15-152]	61 [55-71]	55 [15-152]
ANC (K/uL)		0.8 [0.4-3.3]	1.0 [0.4-3.3]	0.7 (0.6-1.1)
IPSS-M Category	Low Moderate Low Moderate High	2 (40%) 1 (20%) 2 (40%)	2 (100%) 0 (0%) 0 (0%)	0 (0%) 1 (33%) 2 (67%)
ELN 2022 Category	Adverse Intermediate	3 (60%) 2 (40%)	1 (100%) 0 (0%)	2 (50%) 2 (50%)
Prior therapies	No prior therapy HMA +/- venetoclax Intensive chemo	2 (20%) 6 (60%) 2 (20%)	2 (67%) 0 (0%) 1 (33%)*	N/A 6 (86%) 1 (14%)
Lenalidomide Regimen	Monotherapy Combined w/ HMA	8 (80%) 2 (20%)	3 (100%) 0 (0%)	5 (71%) 2 (29%)
Cycles of Lenalidomide Received		13.5 [1-30]	24 [10-30]	4 [1-29]
HSCT		1 (10%)	0 (0%)	1 (14%)

*Induction with CPX-351 followed by lenalidomide maintenance

FIGURE 1. RELAPSE FREE AND OVERALL SURVIVAL FROM TIME OF LENALIDOMIDE INITIATION

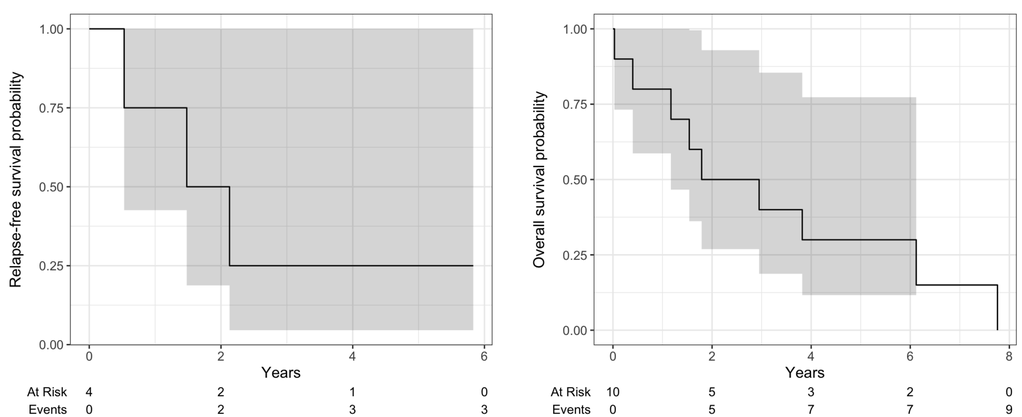


FIGURE 2. LOLLIPOP PLOT OF DDX41 MUTATIONS

- Most common somatic mutation: p.R525H (n=5)
- Most common germline mutation: p.R369G (n=2)
- Various germline frameshift mutations also noted (n=3)
- No patients with known family history of DDX41-associated MN

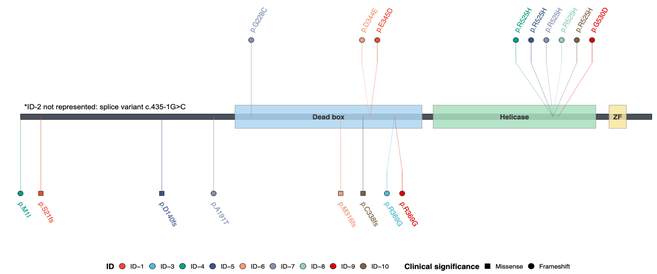
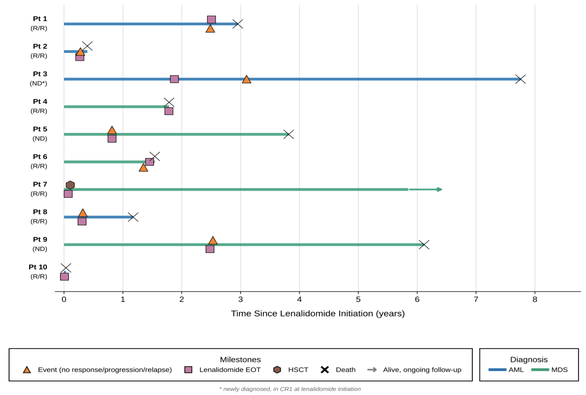


FIGURE 3. CLINICAL TIMELINE OF *DDX41*m MN PATIENTS



GENETIC LANDSCAPE AT MN DIAGNOSIS

- Low frequency of coexisting mutations (n=3)
- Cytogenetics predominantly diploid (n=7) or single abnormal clone (n=2)
- *DDX41*m rarely identified on initial testing (n=2)

BEYOND LENALIDOMIDE

- 3rd-line therapy given in 4 patients after cessation of lenalidomide treatment
- Sepsis was major cause of death (n=6)

TABLE 2. CLINICAL OUTCOMES WITH LENALIDOMIDE-BASEDTHERAPY

		Overall *DDX41*m MN n=10	Newly Diagnosed n=3	Relapsed/Refractory n=7
Response	CR_C*	4 (67%)	1 (100%)	3 (60%)
	CR	3 (50%)	0 (0%)	3 (60%)
	CR_L	1 (17%)	1 (100%)	0 (0%)
	CR_h	0 (0%)	0 (0%)	0 (0%)
	CR_i	0 (0%)	0 (0%)	0 (0%)
	No response*	2 (33%)	0 (0%)	2 (40%)
	Non-evaluable	4 (40%)	2 (67%)	2 (29%)
mRFS (years)		1.8 [95% CI: 0.53 – NR]	Non-calculable	2.13 [95% CI: 1.48 – NR]
mOS (years)		2.37 [95% CI: 1.17 – NR]	6.12 [95% CI: 3.82 – NR]	1.54 [95% CI: 0.4 – NR]

*% of evaluable patients

CONCLUSIONS

- In patients with *DDX41*m MN, lenalidomide demonstrated activity in the absence of concurrent del(5q) in a predominantly R/R population
- Durable RFS suggests lenalidomide may provide meaningful disease control in this genetically defined subset
- Prospective studies are warranted to evaluate the efficacy of lenalidomide both as monotherapy and in combination-based approaches, specifically in *DDX41*m MN

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