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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

The Presence of Ring Chromosomes in Patients with Myeloid Neoplasms Is Predictive of a Poor Outcome

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Cytogenomic analysis is an important tool in the risk stratification of patients with hematologic malignancies. Complex chromosomal alterations are associated with a poor prognosis (Döhner et al., Blood 2022). Ring chromosomes (RC) are circular chromosomal structures associated with loss or gain/amplification of genetic material and are associated with poor prognosis in acute myeloid leukemias (AML) and myelodysplastic syndromes (MDS) (Rosenbaum et al., Human Path 2017). Due to their rarity, the impact of RC on response to therapy has not yet been well characterized. We further examined the significance of RC in AML, MDS and myeloproliferative neoplasms (MPN) by retrospectively analyzing records of patients identified to have RC and myeloid neoplasms at our institution between 2017 and 2023 and collected demographic, diagnostic, treatment, molecular, cytogenomic, and outcomes data.

We identified 27 cases with RC with clinical data available for 25. Demographic and treatment details are described in Table 1. The most common chromosomes involved were r(11) and r(7), 6 and 4 cases respectively, followed by r(6) and r(19) with 2 cases each. The most frequently observed diagnosis was AML in 12 patients (48%) followed by MDS with 9 cases (36%) and MPN in 4 cases (16%). In 17 cases (68%) the RC was cytogenetically detected at diagnosis and was not observed in the context of prior therapy. Remarkably, mutations in TP53 were present in 14 cases (56%) and accompanied by loss of 17p (bi-allelic) in 7 cases (28%). The next most commonly observed gene mutations were in DNMT3A (7 cases), TET2 (4 cases) and ASXL1 (3 cases). In 11 cases (44%) the alterations in TP53 were not associated with prior therapy for other malignancies. The median time from prior chemotherapy to detection of the RC was 5.1 years (range 0.6 to 13.5 years). Chromothripsis (a single DNA catastrophic event resulting in extensive genomic rearrangements of one or a few chromosomes) as detected by CGH+SNP array and homogenous staining regions (autonomously replicating extra-chromosomal elements that are frequently associated with gene amplification) were observed in 3 patients each. RC were the sole genetic abnormality in 5 patients.

A Kaplan-Meier analysis of median overall survival (mOS) in patients with AML and MDS with RC at diagnosis revealed that patients who received supportive care had significantly shorter mOS than patients who received hypomethylating agents (HMA), HMA/Venetoclax(VEN), or anthracycline-based chemotherapy (log rank test, $p = 0.001$). A significant difference in mOS between patients who received HMA alone versus HMA/VEN versus chemotherapy was not observed (11.4 vs 3.1 vs 7.3 months, $p = 0.8$) (Figure 1). Patients who received any of the therapies outlined above likewise demonstrated a significantly longer progression free survival (log rank test, $p = 0.001$). There was no effect on mOS for any of the other tested prognostic parameters, including the presence of a complex karyotype, TP53 allele status, or therapy-related neoplasm, nor for pair-wise interactions between those categories and first-line therapies ($p > 0.05$ for all tested associations).

These data represent a large single-institution cohort of patients with RC and is the first to investigate the impact of therapy and molecular profiles in this population. We observed a high prevalence of TP53 mutations and loss of 17p, however we lacked longitudinal data to make causal inferences regarding the relationship between these abnormalities and ring formation. Of note, 68% of patients did not have prior exposure to therapy, and 36% of all patients lacked TP53 mutations or chromosomal p53 loss, indicating a high rate of de novo ring formation. This is a novel finding perhaps suggesting that inherent chromosomal instability characterizes these patients. Comparing response to type of therapy and outcomes of patients, we conclude that the mOS in patients with RC without therapy is significantly shortened compared with any of the therapeutic options described above, and that the addition of VEN to HMA did not positively influence mOS or PFS compared to HMA alone or chemotherapy in our cohort. Furthermore, the presence of a complex karyotype or a mutation and/or deletion of

TP53 with a RC was not independently associated with inferior mOS, suggesting that the presence of a ring chromosome alone may be an important adverse risk factor in myeloid malignancies.

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Table 1. Demographic and treatment data of patients with ring chromosomes

		All	First line treatment			
			None	HMA	HMA/VEN	Chemo
Sex						
	Female	10 (0.4)	2	2	4	2
	Male	15 (0.6)	4	4	6	1
Diagnosis						
	AML	12 (0.48)	2	3	4	3
	MDS	9 (0.36)	3	3	3	0
	MPN	4 (0.16)	1	0	3	0
Therapy related						
	Yes	8 (0.32)	1	3	3	1
	No	17 (0.68)	5	3	7	2
TP53 alteration						
	None	9 (0.36)	1	2	5	1
	Monoallelic[1]	9 (0.36)	3	3	3	0
	Biallelic[2]	7 (0.28)	2	1	2	2
Complex karyotype						
	Yes	18 (0.72)	5	5	6	2
	No	7 (0.28)	1	1	4	1
Ring identified						
	r(11)	6 (0.23)	2	0	3	1
	r(7)	4 (0.15)	0	0	3	1
	r(6)	2 (0.08)	0	1	1	0
	r(19)	2 (0.08)	0	0	2	0
	Others[3]	12 (0.46)	4	5	2	1
Allo-HSCT						
	Yes	3 (0.12)	0	0	2	1
	No	22 (0.88)	6	6	8	2
Age at detection, yr[4]		73.2 [69.3, 77.4]	75.1 [65.1, 91.0]	76.7 [70.6, 80.3]	71.3 [56.7, 80.1]	53.1 [51.4, 70.9]
Overall survival from detection, mo[4]		5.6 [2.4, 8.9]	0.6 [0.0, 1.2][5]	11.4 [2.8, 20.1]	3.1 [0.0, 11]	7.3 [2.7, 11.9]
Progression free survival from detection, mo[4]		4.4 [1.4, 7.3]	57 [0.0, 1.2][5]	5.9 [5.4, 6.4]	3.1 [0.0, 11.1]	7.3 [2.7, 11.9]

1. Either mutTP53 or delTP53. 2. Both mutTP53 or delTP53. 3. Others: r(9), r(5), r(1q), r(17), r(10), r(4q), r(21), r(3;8), r(13), r(8), unknown, and including 1 patient with two rings identified (n = 26). 4. Values represent medians with 95% CI. 5. p = 0.001 for comparison against all other categories. Allo-HSCT: allogeneic hematopoetic stem cell transplantation. AML: acute myeloid leukemia. Chemo: chemotherapy. Del: deletion. HMA: hypomethylating agent. MDS: myelodysplastic syndrome. Mo: months. MPN: myleoproliferative neoplasm. Mut: mutation. VEN: venetoclax. Yr: years.

Figure 1. Kaplan-Meier analysis of probability of overall survival stratified by first-line treatment after detection of ring chromosome

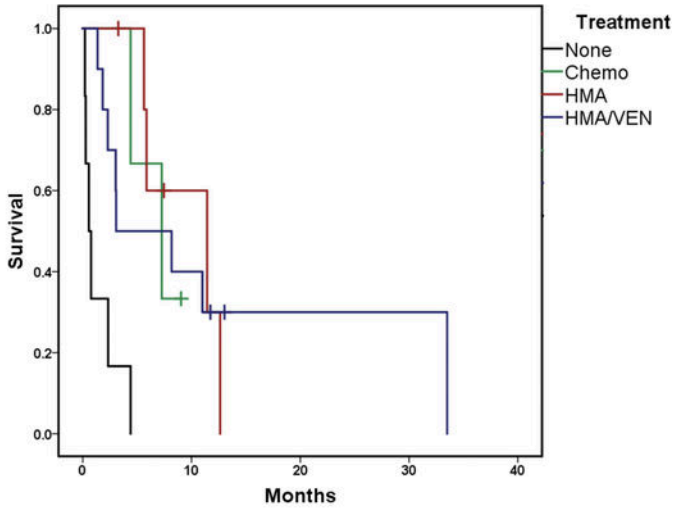

Figure 1

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