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POSTER ABSTRACTS

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

Clinical Significance of Clonal Evolution: A Comparison of Relapsed Versus Refractory Acute Myeloid Leukemia

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Background: Clonal evolution (CE) is a driving force in leukemogenesis, the development of drug resistance, and disease relapse in acute myeloid leukemia (AML). It is unclear whether the detection of clonal evolution is independently predictive of a poorer prognosis. We sought to investigate if AML with higher levels of genetic instability - as evidenced by the presence of clonal evolution - affects prognosis in relapsed and refractory disease.
Patients & Methods: We retrospectively analyzed 207 patients with AML with refractory (128 patients) or relapsed (79 patients) disease from January 1, 2013, to January 1, 2023. A total of 27 patients with refractory disease and 46 patients with relapsed disease had evidence of CE. Cytogenetic and molecular data were obtained at diagnosis and after induction failure or relapse. Baseline demographics including age, sex, race, cytogenetic risk, performance status, and Charlson comorbidity index (CCI) scores were collected at the time of diagnosis, along with the dates of regimen initiation and survival. We compared the OS of those with refractory disease with and without CE and those with relapsed disease with and without CE. Categorical comparisons used Fisher's exact test while the nonparametric Mann-Whitney test was used (where applicable). Normality was assessed by the Shapiro-Wilk test. Ninety-five percent confidence intervals were calculated with the Wilson-Brown Method. Kaplan-Meier survival analyses were computed and compared with log-rank tests. The event for calculation of OS was the date of death with patients otherwise censored at date of last contact.
Results: CE was more common in relapsed disease (46 patients, 58.2%) than in refractory disease (27 patients, 21.1%, $p < 0.001$). There were no significant differences between age, sex, performance status, or CCI scores between all four groups ($p > 0.05$ for all comparisons). At the time of initial diagnosis, CE was more likely to be associated with ELN 2022 adverse-risk AML in the settings of relapsed (OR 8.33; 95% CI: 2.21-31.41, $p = 0.001$) and refractory (OR 2.95; 95% CI: 1.18-7.38, $p = 0.029$) disease. Most patients (74-88%) in each group received intensive chemotherapy consisting either of 7+3, CPX-351, FLAG-IDA, or similar clinical trial protocols with no significant differences between groups ($p > 0.13$). When CE was detected by conventional cytogenetics alone, OS was significantly decreased in refractory disease (4.2 vs. 13.7 months, $p = 0.01$), while unchanged in relapsed disease (8.5 vs 9.1 months, $p = 0.94$). When CE was detected by conventional cytogenetics or molecular techniques, OS trended toward significance in refractory disease (6.4 vs 13.9 months, $p = 0.052$), while OS was unchanged in relapsed disease (8.3 vs 10.7 months, $p = 0.37$).
Conclusion: CE detected in refractory disease is a rarer occurrence - but has an independent negative impact on OS, particularly when detected by conventional cytogenetics. This may be driven by the relative insensitivity of cytogenetic assays (e.g., conventional karyotype, FISH) compared to molecular studies (e.g., next-generation sequencing), as the burden of CE must be relatively higher to be recognized by the cytogenetic techniques. In contrast, most patients with relapsed disease had CE detected; however, it had no independent effect on survival. The poor prognosis at disease relapse is likely driven by the relapse itself rather than a change in leukemic drivers.

Disclosures Maher: *Sobi (Doptelet):* Speakers Bureau; *Bristol Myers Squibb:* Membership on an entity's Board of Directors or advisory committees.

A. Baseline demographics of relapsed and refractory AML with and without clonal evolution

		Refractory disease				Relapsed Disease			
		Clonal Evolution		No Clonal Evolution		Clonal Evolution		No Clonal Evolution	
N		27	21.1%	101	78.9%	46	58.2%	33	41.8%
Male sex - no. (%)		11	40.7%	54	53.5%	23	50.0%	15	45.5%
Age at Diagnosis - year									
	Median	64.1		61.98		59.1		60.5	
	Range	22.7-78.6		20.7-81.8		19.8-76.4		32.1-76.0	
Race-no.(%)*									
	Black	9	33.3%	26	25.7%	18	39.1%	6	18.2%
	White	16	59.3%	70	69.3%	24	52.2%	24	72.7%
	Other	2	7.4%	5	5.0%	4	8.7%	3	9.1%
ELN 2022 Cytogenetic risk group - no. (%)#									
	Favorable	2	7.4%	11	10.9%	14	30.4%	14	42.4%
	Intermediate	6	22.2%	39	38.6%	10	21.7%	16	48.5%
	Adverse	19	70.4%	45	44.6%	20	43.5%	3	9.1%
	Unknown	0	0.0%	6	5.9%	2	4.3%	0	0.0%
CCI-Score^									
	Median	4		4		4		5	
	Range	2-11		2-9		2-14		2-7	
ECOG at diagnosis									
	Median	1		1		1		1	
	Range	0-3		0-4		0-3		0-3	
ECOG at diagnosis of R/R disease									
	Median	1		1		1		1	
	Range	0-3		0-3		0-3		0-3	

*1 unknown race refratory CE
#6 unknown in Refractory NCE and 2 unknown Relapsed CE
^1 unknown in Relapsed CE

B. Overall survival of clonal evolution versus no clonal evolution in refractory disease

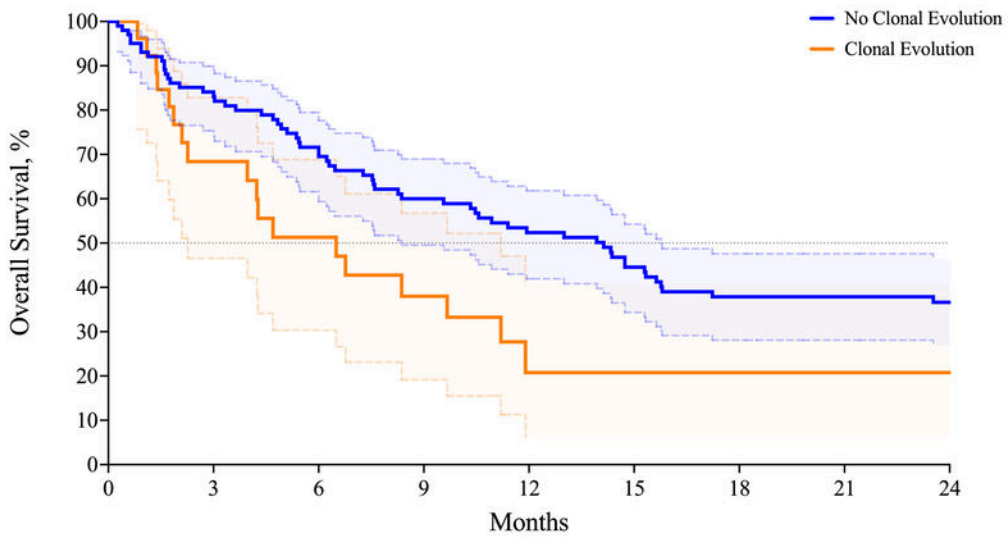

Figure 1

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