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POSTER ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Patterns of Relapse in Patients with Acute Myeloid Leukemia (AML) Treated with Venetoclax-Containing Regimens

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Background:
Advances in next generation sequencing (NGS) technologies and better insight into the biology of acute myeloid leukemia (AML) have demonstrated the heterogeneity of the disease and its polyclonal nature at the time of diagnosis. While targeted therapies have improved remission rates and significantly improved outcomes, relapses are frequent and tend to arise from resistant sub-clones with genomic profiles and sensitivities that are often different from the dominant clone at initial diagnosis. While the use of targeted therapy at initial diagnosis may effectively control the dominant clone, the backbone chemotherapy in combination may be important in controlling the myriad of sub-clones that may be present.
Methods:
We hypothesized that the type of chemotherapy used in combination with the BCL2 inhibitor venetoclax (ven) may influence the pattern of relapses (including genomic profile) in patients with AML treated with different regimens. We retrospectively reviewed patients treated in three clinical trials of frontline ven in combination with chemotherapy-cladribine (clad) + LDAC + ven, CLIA + ven, and FLAG-IDA + ven-who had documented relapsed disease at any time. All patients had undergone karyotype and NGS based mutation testing at baseline and at time of relapse. We analyzed the baseline characteristics, karyotypes, and mutational profiles at baseline and at the time of relapse as well as outcomes of these patients.
Results:
We retrospectively reviewed 34 newly diagnosed patients who were treated on three prospective clinical trials including frontline ven and experienced a relapse: clad + LDAC + ven (N=19); CLIA + ven (N=7); and FLAG-IDA + ven (N=8). The median ages of these patients were 68 yrs (range, 57-80), 43 (23-61), and 39 (20-63), respectively. The median durations of response for these relapsing patients on each of the trials were 4.80, 8.05, and 7.61 months, respectively. 5.3%, 0%, and 75% of patients who relapsed from each of the three groups, respectively, had undergone prior allogeneic SCT. The baseline and relapsing mutation frequencies for the patients from each of the trials are summarized in Table 1.
The most prevalent mutations present in patients who relapsed after frontline clad + LDAC + ven were TP53 (32%) and TET2 (26%); on CLIA + ven, DNMT3A (57%) and TET2 (43%); on FLAG-IDA + ven, TP53 (50%) and DNMT3A (38%). In the three cohorts, among all newly acquired mutations (n=41), the highest incidences were observed in RUNX1 (22%), DNMT3A (17%), TET2 (10%), and SMC3 (10%) (Table 1). The relapsed clad + LDAC + ven cohort developed the greatest variety of intermediate- and unfavorable-risk cytogenetic abnormalities upon relapse, and of the 42% of patients (n=8) with new abnormalities, -7/7q- was most frequently observed at 38% (n=3). Among all newly acquired cytogenetic abnormalities at relapse among the three cohorts, 55% (n=6) acquired -7/7q-, making this the most frequent cytogenetic abnormality acquired upon relapse in these patients.
Conclusions:
Among patients with relapsed AML after treatment with 3 frontline ven-containing regimens, we observed varying profiles. Mutational profiles exhibiting previously undetected aberrancies in RUNX1, DNMT3A, TET2, and SMC3 were most frequently observed at the time of relapse. Meanwhile, the most frequent karyotypic changes observed at the time of relapse were the acquisition -7/7q among patients, with the greatest number of acquisitions occurring among the clad + LDAC + ven cohort.

Further analysis of the patterns of genomic changes at the time of relapse, including after treatment with hypomethylating agents and ven, can inform treatment decisions, maintenance strategies, and can improve patient outcomes

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Table 1: Mutational and cytogenetic profiles in patients with AML after relapse on venetoclax-containing regimens

	clad + LDAC + ven, relapse		**CLIA + ven, relapse**		**FLAG-IDA + ven, relapse**		**All trials, relapse**	
Mutation	Prevalence	Acquired mutations (N)	Prevalence	Acquired mutations (N)	Prevalence	Acquired mutations (N)	Prevalence	Acquired mutations (N)
RUNX1	16%	2	29%	3	25%	4	22%	9
SMC3	0%	0	29%	2	13%	2	10%	4
DNMT3A	11%	2	57%	1	38%	4	17%	7
TET2	26%	0	43%	1	25%	3	10%	4
TP53	32%	-2	0%	0	50%	1		-1
Cytogenetics								
-7/7q-	32%	3	14%	1	25%	2	55%	6
abn11q	32%	1	0%	-1	25%	2	18%	2
+8	16%	2	0%	-1	25%	0	9%	1
-5/5q-	16%	1	0%	0	13%	0	9%	1
-17/17q-	0%	1	0%	0	0%	0	9%	1

clad = cladribine, LDAC = low dose cytarabine, ven = venetoclax, FLAG-IDA = fludarabine, cytarabine, idarubicin and G-CSF

Figure 1

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