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ORAL ABSTRACTS

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

Fms-like Tyrosine Kinase 3 Ligand Kinetic Profile Is the Strongest Factor Predicting Refractoriness after Induction and Event-Free Survival in Adults with AML: A Filo Prospective Multicentric Study

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Background: Recently, a monocentric study has shown in adults with a non-previously treated acute myeloid leukemia (AML) that the stagnation of low levels of Fms-like tyrosine kinase 3 ligand concentration (FLc) in plasma, up to day 22 after an intensive induction, was associated with refractoriness and lower survivals (Peterlin et al, 2021). The present study wanted to confirm these results prospectively on a larger cohort of patients and in a multicentre way.
Methods: This was a prospective non-interventional multicentre investigator sponsored trial (FLAMVAL study, clinicaltrials.gov: NCT04641910. One of the main objective was to study the impact on various outcomes of FL levels, evaluated during an intensive induction, in adults (>=18 year (y) old) with a non-previously treated non-M3 AML. Patients could receive a standard intensive induction chemotherapy combining anthracycline + cytarabine as part of a trial or not. Outcomes to be studied were responses, 1y overall survival (OS) and event-free survival (EFS), and 1-y leukemia-free survival (LFS) and relapse in responders. Response was evaluated according to ELN2017 criteria at day+30 after induction. Using a new cytokine multiplex assay from Milliplex (MILLIPLEX®), FL levels (expressed in pg/mL) were evaluated at Day (D) 1, D8, D15 and D22 from Day 1 of induction.

Results: Between June 2021 and August 2022, 226 patients from 16 FILO centres were included but 204 with full evaluation of FL levels (816 samples) were considered for analyses. Their characteristics are reported in **Table 1**. At the time of analysis (July 2023), 1-y OS, EFS and LFS were 87+-5%, 78.3+-6% and 59.8+-8%, respectively.
Median [Q1-Q3] FLc were 1.22 [0-4.19] at D1, 13.83 [2.26-72.46] at D8, 128.55 [13.06-293.43] at D15 and 24.14 [4.60-155.14] at D22. The number of refractory patients was significantly higher for those patients with a FLc < median at Day 8 (30.4% vs 13.7%, p=0.01), D15 (35.6% vs 8%, p<0.001) and D22 (31.1% vs 12.9%, p=0.007). 1-y OS and LFS were similar between patients with a FLc < or >= median at the four times considered. This was true also for 1y-EFS at D1 and D22. However, 1-y EFS was significantly worse for those with a FLc < median at D8 (48.5 % (41-55) vs 31 % (25-37), p=0.004) and at D15 (47.6 (40-55) vs 31% (25-37), p=0.002).
As reported before (Peterlin et al, 2021), all patients but 4 (with a decrease of levels all along) can be categorized according to three FLc kinetic profiles: i) sustained increase from days 1 to 22 (FLI group n=39, 19% of the cohort), ii) increase from days 1 to 15, then decrease at day 22 (FLD group, n=86, 42% of the cohort) and iii) stagnation of low levels all along (<100 pg/mL from days 1 to 22, FLL group, n=75, 37% of the cohort). OS and LFS were similar between these three groups while 1-y EFS was significantly lower for the FLL group (45% [33; 57]) compared to FLI and FLD groups (64% [49; 79] and 71% [61; 80], p<0.001) (**Figure 1**). This difference was due to a higher proportion of refractory patients in the FLL group (n=45/75 42.7% vs FLI =5/39, 12.8% vs FLD n=8/86, 9.3%, p<0.001, 2 patients not evaluated for response). Similar incidence of relapse was observed for responders comparing the three groups. Interestingly, only 8.8% (n=11/125) of the FLI/FLD patients had a FLc level <100 pg/ml at both times D8 and D15, suggesting that a FLL status can be predicted as soon as D15.
For multivariate analyses, we compared FLc kinetic profiles (FLL vs FLI/FLD) on one hand and FLc medians (D1 D8 D15 and D22) on the other hand with other factors associated with a p value <0.20 by univariate analyses. In both models, only FLc kinetic profile and medians together with ELN2017 classification were found to be independent factors predicting response and EFS. However, FLL status was the strongest factor associated with refractoriness (OR: 6.2, 95%CI: 2.94-13.73, p<0.001, ELN favorable vs Intermediate p=0.003, favorable vs adverse p=0.002) and lower EFS (OR: 2.58, 95%CI: 1.40-4.79, p=0.002, ELN p=0.01 and 0.004).
Conclusion: This large prospective multicentre trial confirms that a stagnation of low levels of FLc during a first-line induction in adults with non-M3 AML is the strongest factor (above ELN classification) associated with refractoriness and lower EFS in these patients. The study suggests also that this simple test could be useful to envisage salvage therapy including allotransplant just after D15 of induction.

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Table 1: Patients' characteristics

At baseline	
All (n=204)	
Age	
- Median y.o [Q1-Q3]	59 [48-67]
- </ ≥60 yo n= (%)	106 (52)/98 (48)
Sex (Male/Female) n= (%)	105 (51)/99 (49)
Blasts (median,% [Q1-Q3] , marrow)	48 [29.5-75]
WBC Giga/L, median [Q1-Q3]	4.09 [2.085-11.225]
< />=20 Giga/L n= (%)	175 (71)/29 (29)
AML WHO (n, %)	
- with myelodysplasia-related changes	28 (14)
- with recurrent genetic abnormalities	57 (28)
- NOS	116 (57)
- Therapy-related myeloid neoplasms	2 (1)
- Myeloid sarcoma	1 (0)
ELN 2017 (n, %)	
- Favorable (n=, %)	56 (27)
- Intermediate (n=, %)	87 (43)
- Adverse (n=, %)	61 (30)
FLT3-ITD (n, %)	40 (20)
FLT3 TKD (n, %)	7 (3)
Both (n, %)	1 (0)
Intensive induction	
Standard n= (%)	200 (98%)
CPX-351 n= (%)	5 (2.5%)
As part of a trial n= (%)	120 (59%)
Induction + FLT3 Inhibitor n= (%)	41 (20%)
Induction + lomustine n= (%)	24 (12%)
Induction + dexamethasone n= (%)	1 (0.5%)
Induction + dasatinib n=(%)	1 (0.5%)
Induction + tocilizumab n=(%)	5 (2.5%)
Status after induction	
- Responders n= (%))	157 (132+16+9) (77%)
- Refractory n = (%)	45 (22%)
- Not evaluated n= (%)	2(1%)
FLc kinetic profile	
FLI n= (%)	39 (19%)
FLD n= (%)	86 (42%)
FLL n= (%)	75 (37%)
Not classified n= (%)	4 (2%)

Figure 1: Event-Free-Survival according to the three FLc kinetic profile groups (FLL vs FLI vs FLD)

Figure 1