Impact of Somatic Mutations on Treatment Response and Outcomes in Patients with Core Binding Factor Acute Myeloid Leukemia

Somedeb Ball[1], Akriti G Jain[1], Parth Patel[2], Chen Wang[2], Luis E Aguirre[1], Zaker I Schwabkey[1], Mohammad Hussaini MD[3], Onyee Chan[4], Seongseok Yun[4], Andrew T Kuykendall[4], Eric Padron[4], Kendra Sweet[4], Jeffrey E Lancet[4], Rami S Komrokji[4], **David A Sallman**[4].

[1] Department of Hematology and Medical Oncology, University of South Florida/H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA
[2] Department of Internal Medicine, University of South Florida, Tampa, FL, USA
[3] Department of Hematopathology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA
[4] Department of Malignant Hematology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

Abstract

CONTEXT: Prognostic significance of somatic mutations remains unclear in patients (pts) with core binding factor acute myeloid leukemia (CBF-AML).

METHODS: In this single center retrospective study, clinical and molecular data were collected on adult pts with CBF-AML.

RESULTS: Among 59 pts with CBF-AML [t (8;21), n=21 and Inv (16), n=38], most common mutations were *KIT* (31%) and *NRAS* (26%). Rates of CBF-MRD negativity and relapse (17%) were similar with or without ≥ 1 of *KIT*, *RAS*, or *FLT3* mutations. Presence of any of these 3 mutations was associated with worse relapse free survival (7.7 vs. 12.9 months; p= 0.01), with no significant difference in overall survival.

CONCLUSION: Mutations in *KIT*, *RAS*, and *FLT3* are enriched in CBF-AML and contribute to earlier relapse in pts.

Background

- Core-binding factor acute myeloid leukemia (CBF-AML), including t(8;21) and Inv(16), constitutes 15% of all AML cases and generally carries a favorable prognosis
- However, relapse rate is ≈ 30% and predictors are not well understood
- Advancement in next generation sequencing (NGS) has led to identification of multiple somatic mutations in CBF-AML
- Prognostic significance of recurrent somatic mutations in pts with CBF-AML remains unclear

Objective

- To estimate the incidence and distribution of recurrent somatic mutations in pts with CBF-AML
- To assess the impact of somatic mutations on overall outcomes in pts with CBF-AML

Materials & Methods

- Single center retrospective study
- Clinical, demographic, and molecular data were collected from adult pts with CBF-AML who were treated at Moffitt Cancer Center.
- We included pts with results available for MRD by polymerase chain reaction (PCR) for CBF abnormality (CBF-MRD) from time of induction and consolidation
- All statistical analyses were performed in SPSS

Table 1. Key Characteristics of Study Population

Characteristics	Total n=59	t(8;21) n=21	Inv (16) n=38	P value
Age in years at diagnosis	48 (24-74)	49 (27-74)	47 (24-71)	0.67
Male gender	30 (51%)	12 (57%)	18 (47%)	0.47
WBC count	31 (1.3-165.7)	11.5 (1.9-33.2)	**43.2** (1.3-165.7)	**0.01**
BM Blasts	53% (6%-95%)	59% (6%-87%)	51% (9%- 95%)	0.16
EM disease	3 (5%)	2 (10%)	1 (3%)	0.54
Relapse	10 (17%)	2 (10%)	8 (21%)	0.46
Allo- SCT	23 (39%)	8 (38%)	15 (39%)	0.91
Mutational Distribution at Baseline (n= 54)				
KIT	17 (**31%**)	9 (**45%**)	8 (24%)	0.13
NRAS	14 (**26%**)	3 (15%)	11 (**32%**)	0.13
KRAS	8 (15%)	2 (10%)	6 (18%)	0.69
FLT3-TKD	6 (11%)	1 (5%)	5 (15%)	0.39
FLT3-ITD	5 (9%)	3 (15%)	2 (6%)	0.36
Kinase mutations (*KIT*/*RAS*/*FLT3*)	40 (**74%**)	15 (75%)	25 (74%)	0.72
NGS negative	9 (17%)	3 (15%)	6 (18%)	1.00

Results

- Most common mutations at diagnosis included *KIT* (31%), *NRAS* (26%), *KRAS* (15%), *FLT3-TKD* (11%), and *FLT3-ITD* (9%). (**Table 1**)
- Mutations in *NRAS* were enriched (32%) in Inv (16) AML, whereas *KIT* mutations were common (45%) in association with t (8;21).
- Most common induction regimen was "7+3" (48%) and "7+3+GO" (37%); 36% received GO consolidation (median- 3 cycles) (**Table 2**)
- Overall, 23 (39%) pts underwent allogeneic stem cell transplant (allo-SCT), with no difference in respect to baseline mutations

Table 2. Treatment Response in CBF-AML by Subtypes

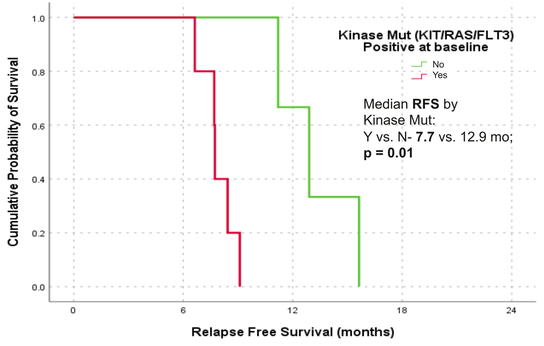
Parameter	Total n=59	t(8;21) n=21	Inv (16) n=38	P value
Induction regimen				0.27
7+3	28 (48%)	7 (33%)	21(55%)	
7+3+GO	22 (37%)	10 (47%)	12 (32%)	
Others	9 (15%)	4 (19%)	5 (13%)	
GO schedule in induction				0.09
Day 1 only	14 (24%)	8 (38%)	6 (16%)	
Days 1,4, and 7	11 (19%)	2 (10%)	9 (24%)	
GO in consolidation	21 (36%)	8 (38%)	13 (34%)	0.66
No. of consolidation cycles				
</=2	16 (27%)	7 (33%)	9 (24%)	0.35
>2	39 (66%)	12 (57%)	27 (71%)	
CBF-MRD negative after induction*	6 (15%)	1 (7%)	5 (19%)	0.39
NGS neg after induction*	16 (67%)	5 (56%)	11 (73%)	0.41
Post-induction clearance of kinase mutations*	18 (100%)	8 (100%)	10 (100%)	
CBF-MRD neg after induction and consolidation*	33 (70%)	9 (56%)	24 (77%)	0.18

* Calculated on number of evaluable patients for the parameter

Results

- CBF-MRD negativity was 15% post-induction and 70% post-consolidation, with no significant difference with or without kinase mutations (*KIT*/*RAS*/*FLT3*)
- In t(8;21) AML, CBF-MRD negativity rate was lower in *KIT*-mutant (38% vs. 75%) pts, although not statistically significant (p = 0.31)
- Baseline kinase mutation was associated with worse relapse free survival (mRFS- 7.7 vs. 12.9 m; p= **0.01**) (**Figure 1**), with no difference in overall survival (mOS- 94.1 m vs. not reached, p=0.44).

Figure 1. Relapse Free Survival in CBF-AML



Conclusions

- Mutations in *KIT*, *RAS*, and *FLT3* are common in CBF-AML
- Baseline kinase mutation (≥ 1 of *KIT*, *RAS*, or *FLT3)* was associated with a shorter RFS in pts with CBF-AML
- Rates of CBF-MRD negativity, relapse, and allo-SCT did not differ significantly between mutational subgroups
- There was no difference in OS with or without baseline kinase mutations

Presented at *SOHO 2022* Annual Meeting, Houston, TX, USA; **Corresponding Author: Dr. Somedeb Ball, MD, H. Lee Moffitt Cancer Center and Research Institute; Email: somedeb.ball@moffitt.org**