Prognostic Impact of *ASXL1* Mutations in Chronic Phase Chronic Myeloid Leukemia

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Abstract

Context: Mutations in *ABL1* are established risk factors for therapy resistance in chronic phase chronic myeloid leukemia (CML-CP). However, much less is known about the impact of other cancer-associated gene mutations.

Objective: Study the prevalence and clinical impact of cancer-associated gene mutations in CML-CP.

Design: We screened our databases for CML-CP patients who were tested with a targeted next-generation sequencing panel that included 81 genes recurrently mutated in hematologic malignancies. Event-free survival (EFS) was measured from treatment initiation to the time of an event defined as loss of hematologic response, loss of major cytogenetic response (MCyR), lack of MCyR after 12 months, or transformation to accelerated/blast phase. Failure-free survival (FFS) was measured similarly, with the additional events of drug discontinuation due to adverse effects or no response. We subsequently performed univariate and multivariate analyses.

Results: The median age of patients was 60 years (18–80) and 46% were female. The most common first-line therapy was dasatinib (52%), followed by imatinib (19%), dasatinib + venetoclax (16%), and other TKIs (13%). The distribution of evaluable patients to low, intermediate, and high Sokal groups was 21%, 61%, and 18%, respectively. Cancer mutations were found in 23/68 patients (34%). The most common mutations involved *ASXL1* (10/68 patients; 15%), *DNMT3A* (5/68 patients; 7%), and *RUNX1* (3/68 patients; 4%). Mutations were also detected in *ASXL2*, *CALR*, *EZH2*, *GNAS*, *IDH2*, *SF3B1*, *SMC3*, *SRSF2*, *STAG2*, and *SUZ12*. Unlike mutations in other genes, patients with *ASXL1* mutations had worse EFS compared to the no-mutation group (median of 33 vs. 88 months; *P*=0.002) and worse FFS (median of 14 vs. 58 months; *P*=0.04). There was no difference in overall survival by mutational status. In a multivariate analysis, mutated *ASXL1* was independently associated with worse EFS (HR of 4.42; 95% CI 1.63–11.99). There was a non–statistically significant trend of lower molecular response rates and longer times to response (TTR) in *ASXL1*-mutated patients compared to wild-type (major molecular response rate of 78% vs. 82%; *P*=0.7 with median TTR of 17.5 vs. 9.2 months; *P*=0.5).

Conclusion: Mutations in *ASXL1* are associated with delayed responses and worse outcomes when detected in CML-CP.

Background

- The clinical impact of mutations in the *ABL1* gene on response to therapy in chronic phase chronic myeloid leukemia (CP-CML) is well established.
- Less is known about the impact of mutations in other cancer-associated genes.

Objective

- Study the prevalence and clinical impact of cancer-associated gene mutations in CML-CP.

Design

Patients and mutations

- Retrospective analysis of 68 CML-CP patients, who underwent mutational testing at MD Anderson Cancer Center.
- Testing was done through targeted next-generation sequencing of 81 genes recurrently mutated in myeloid malignancies.

Survival analysis

- Event-free survival (EFS) with events defined as:
  - Loss of hematologic or major cytogenetic response (MCyR)
  - No MCyR after 12 months of treatment
  - Transformation to accelerated / blast phase
  - Death
- Failure-free survival (FFS): same as EFS + drug discontinuation due to adverse effect or no response.
- Univariate and multivariate analyses for EFS.

Results

Characteristics	Patients N=68
Age, years	60 (18-80)
Female	31 (46%)
Sokal score	
Low	12/56 (21%)
Intermediate	34/56 (61%)
High	10/56 (18%)
1st line treatment	
Imatinib	13 (19%)
Dasatinib	35 (52%)
Other	20 (29%)
Mutations per patient	
0 mutations	45 (66%)
1 mutation	17 (25%)
≥ 2 mutations	6 (9%)

Values are either N (%) or median (range)

Sokal score reported as number/evaluable (%).

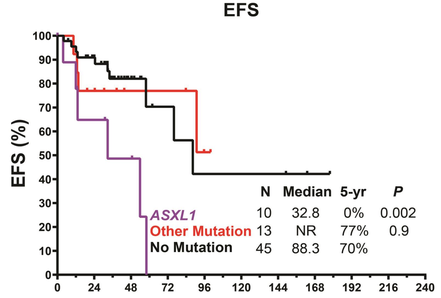
Mutation	N (%)
ASXL1	10 (15%)
DNMT3A	5 (7%)
RUNX1	3 (4%)
ASXL2	1 (2%)
CALR	1 (2%)
EZH2	1 (2%)
GNAS	1 (2%)
IDH2	1 (2%)
SF3B1	1 (2%)
SMC3	1 (2%)
SRSF2	1 (2%)
STAG2	1 (2%)
SUZ12	1 (2%)

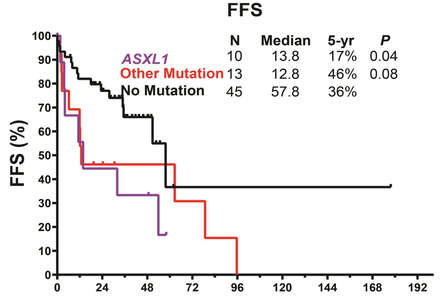
Response	No Mutation N (%)	No Mutation Median TTR[1] (range)	*ASXL1* N[2] (%)	*ASXL1* Median TTR (range)	*ASXL1* *P*	Other Mutations N (%)	Other Mutations Median TTR (range)	Other Mutations *P*
MCyR	44 (98%)	3.4 (1 – 52)	9 (100%)	3.3 (1 – 65)	0.9	12 (92%)	3.7 (1– 13)	0.4
CCyR	41 (91%)	6.0 (2 – 31)	8 (89%)	9.7 (3 – 66)	0.9	11 (85%)	6.0 (3 – 13)	0.6
MMR	37 (82%)	9.2 (3 – 142)	7 (78%)	17.5 (5 – 66)	0.7	10 (77%)	6.7 (3 – 70)	0.7
MR4	30 (67%)	16.2 (3 – 167)	5 (56%)	29.1 (10 – 86)	0.7	8 (62%)	15.4 (4 – 76)	0.7
MR4.5	24 (53%)	17.1 (4 – 73)	4 (44%)	48.7 (11 – 89)	0.7	8 (62%)	27.0 (12 – 120)	0.8
BCR::ABL <10% at 3 months	27/41 (66%)	-	3/9 (33%)	-	0.1	5/12 (42%)	-	0.2

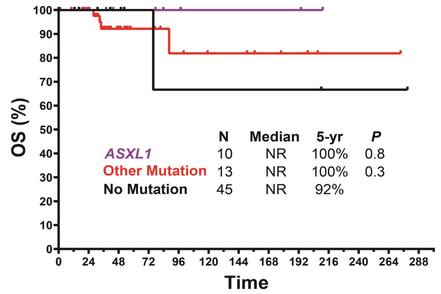
TTR, Time to response; MCyR, major cytogenetic response; CCyR, complete cytogenetic response; MMR, major molecular response

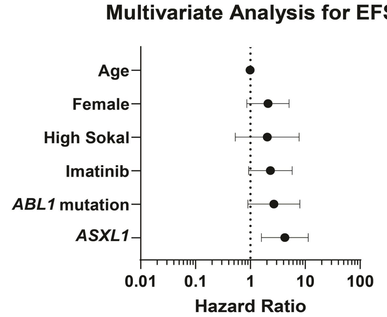
[1] TTR reported in months; no statistically significant differences when comparing TTR

[2] Only 9 patients were evaluable









Conclusions

- Mutations in *ASXL1* are associated with delayed responses in CML-CP.
- Mutations in *ASXL1* are associated with worse EFS and FFS.

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