CSF3R-mutated chronic neutrophilic leukemia: a two-center study of 44 consecutive patients

CSF3R mutations (*CSF3R*^{MUT}), most commonly T618I, represent the defining genomic alteration in chronic neutrophilic leukemia (CNL) and is present in ~80% of cases.[1-4] Although relatively few studies have explored disease characteristics, both the largest population-based study utilizing SEER and NCBI databases and Mayo Clinic study of 19 consecutive *CSF3R*-mutated CNL (*CSF3R*^{MUT}-CNL) patients have played a major role in describing the clinical manifestations and outcomes. These studies highlighted prognostic indices such as age, baseline white blood cell (WBC) count >60×10^9/L, platelet <60×10^9/L and the presence of *ASXL1* mutations.[2,5]

Despite these reports, data on treatment outcomes and prognostic factors remain limited due to the rarity of CNL. In this two-center retrospective study, we examined clinical and molecular predictors of treatment response, overall survival (OS), and blast transformation (BT) in *CSF3R*^{MUT}-CNL patients diagnosed at the Mayo Clinic (USA) and the University of Montreal (Canada) using the International Consensus Classification criteria.[6] We also assessed outcomes following allogeneic stem cell transplantation (ASCT).

The study was approved by the institutional review boards of both institutions. Electronic medical records were reviewed to identify patients and extract relevant data. Categorical and continuous variables were summarized using frequencies (%) and medians (range). Kaplan-Meier estimates (with log-rank tests) and Cox regression models were utilized to identify predictors of OS and BT. Statistical analyses were performed using JMP Pro 17.0.0 software (SAS Institute, Cary, NC, USA).

Forty-four patients diagnosed between October 1995 and April 2025 were included. The median age at diagnosis was 68 years (range, 26-93) and 30 (68%) were male. *CSF3R*^{MUT}/ variants included 39 (89%) with T618I, two (5%) with M696T, and one (2%) each with I598I, Q739*, and T640N. Seven of the 39 patients with *CSF3R*^{T618I} had additional *CSF3R*^{MUT}. Frequent co-mutations involved *ASXL1* in 25 (60%) patients, *SETBP1* in 14 (36%), and *SRSF2* in eight (31%), with overlapping occurrence. Of the 26 patients who had data available for all three co-mutations, ten (38%) had ≥2. Further details of baseline characteristics are shown in Table 1 and Figure 1.

Ten patients (median WBC 29×10^9/L [range: 19-58]) were initially observed without treatment for a median of 8.6 months; two remained on observation alone at 46 and 77 months. Hydroxyurea monotherapy was the most common first-line therapy, used in 26 (65%) patients. Other first-line regimens included ruxolitinib or ruxolitinib-based combinations (Ruxo/Ruxoc), as well as other agents such as tyrosine kinase inhibitors (imatinib and dasatinib), immunomodulatory drugs, interferon, and azacitidine, as detailed in *Online Supplementary Table S1*. Second-line therapies comprised Ruxo/Ruxoc in 12 (42.8%) patients and hydroxyurea alone or in combination with other agents excluding ruxolitinib (HU/HUc) in eight (28.6%) patients. A WBC response, defined as a ≥50% reduction from baseline, was achieved in 21 (78%) patients treated with HU/HUc *versus* nine (60%) treated with Ruxo/Ruxoc (*P*=0.2); further details of treatment response are provided in *Online Supplementary Table S1*. WBC response to HU/HUc was lower with abnormal karyotype (2 [40%] *vs*. 17 [94%]; *P*=0.02). Among those who had Ruxo/Ruxoc, WBC response was lower in patients with *SETBP1*^{MUT} (0% *vs*. 9 [72%]; *P*=0.05) and males (4 [40%] *vs*. 5 [100%]; *P*=0.04).

At a median follow-up of 44 months for living patients, disease transformation occurred in ten patients, including seven with BT (6 with T618I and 1 with T640N) and three with chronic myelomonocytic leukemia (2 with M696T and 1 with T618I). BT rate at 2, 3, and 5 years was 15%, 31%, and 43%, respectively. Univariate analysis (UVA) identified male sex (*P*<0.01), >5% immature WBC (*P*=0.045), platelets <160×10^9/L (*P*=0.04), and presence of *ASXL1* or *SETBP1* mutation (*ASXL1*^{MUT}/*SETBP1*^{MUT}) (*P*<0.01) as risk factors for BT, *Online Supplementary Table S2*. On multivariable analysis (MVA), only *ASXL1*^{MUT}/*SETBP1*^{MUT} remained significant.

Median OS was 26 months (95% confidence interval [CI]: 21-43) for the entire cohort; 24 months for patients with T618I *CSF3R*^{MUT} *versus* 53 months for those with other *CSF3R*^{MUT}; *P*=0.1. In UVA, age >60 years (hazard ratio [HR]=5.1; *P*<0.01), WBC >50×10^9/L (HR=2.6; *P*=0.02), platelets <160×10^9/L (HR=3.6; *P*<0.01) and *ASXL1*^{MUT}/*SETBP1*^{MUT} (HR=4.2; *P*=0.03) were associated with shorter OS, *Online Supplementary Table S2*. In MVA, age >60 years (HR=6; *P*=0.03), WBC >50×10^9/L (HR=12; *P*<0.01), and *ASXL1*^{MUT}/*SETBP1*^{MUT} (HR=9.5; *P*=0.01) remained significant.

Based on the HR on MVA, one adverse point was allocated for age >60 years, and two adverse points each for WBC >50×10^9/L and *ASXL1*^{MUT}/*SETBP1*^{MUT}. Patients were accordingly stratified into low- (0-2 points), intermediate- (3) and high- (4-5) risk groups, with corresponding median OS of "not reached", 29 months, and 16 months (*P*<0.01), Figure 2. Causes of death included disease progression (82%), infection/bleeding (9%), and ASCT complications (9%).

Seven patients underwent ASCT, including two after BT. Four (57%) of the seven remain alive, including two without evidence of disease (both 45 months post-ASCT; 1 harbored *ASXL1*^{MUT}) and the other two with active disease (both harbored *ASXL1*^{MUT}). Three patients died, one each from veno-occlusive disease (day +34), CNS relapse with AML (105 months post-ASCT), and unrelated causes (44 months post-ASCT).

These outcomes are consistent with findings in prior studies, suggesting that ASCT offers long-term survival in an otherwise aggressive disease with limited treatment options.[5,7-9] In one study, although none of the five patients responded to pre-transplant treatments, four achieved complete remission after transplantation and two remained in remission at 362 and 441 days post-ASCT.[7] Similarly, the population-based study by Ruan *et al*. reported good outcomes in two patients who had ASCT, both remaining alive after 5 years.[5] In our cohort, transplanted patients had significantly superior median OS compared to non-transplanted patients (115 *vs*. 23 months; *P*=0.03), further strengthening the argument for early transplant referral, particularly in patients with high-risk features.[10]

Table 1. Baseline characteristics of patients with chronic neutrophilic leukemia.

Variable	All N (%)	*CSF3R*^{T618I} N=39 N (%)	Others N=5 N (%)	*P*	OR (95% CI)
Sex: male	30 (68.2)	28 (71.8)	2 (40.0)	0.3	0.27 (0.02-2.70)
Median age at diagnosis, years*	68 (26-93)	68 (33-93)	59 (26-72)	0.1	0.95 (0.90-1.01)
Median variant allele frequency*	43 (5-51.4)	43 (5–51.4)	21	0.2	0.9 (0.8-1.1)
Presence of symptoms at diagnosis	16 (44.4)	16 (48.5)	0	0.23	NA
Prior leukocytosis before diagnosis	21 (50)	19 (51.4)	2 (40.0)	1	0.64 (0.05-6.27)
Prior cytotoxic therapy	6 (13.6)	5 (12.8)	1 (20.0)	0.5	1.7 (0.03-22.6)
Family history of hematological neoplasm	18 (52.9)	15 (48.4)	3 (100.0)	0.22	NA (0.38-NA)
History of thrombosis	6 (14.6)	6 (16.7)	1 (20.0)	1	NA
History of hemorrhage	8 (18.6)	8 (21.1)	0 (0.0)	0.56	NA
Sweet syndrome	3 (7.0)	3 (7.9)	0 (0.0)	1	NA
Splenomegaly	28 (66.7)	26 (70.3)	2 (40.0)	0.31	0.3 (0.02-2.9)
Hepatomegaly	7 (17.1)	5 (13.9)	2 (40.0)	0.2	3.9 (0.3-44.9)
Lymphadenopathy	4 (9.8)	4 (11.1)	0 (0.0)	1	NA
Hemoglobin, g/dL*	11.2 (6.4-16.1)	10.8 (6.4-16.1)	12.7 (11.4-16)	0.1	1.5 (0.94-2.5)
Platelet, x10^9/L*	190 (25-476)	168 (25-476)	250 (243-362)	0.14	1.01 (1-1.02)
Leukocyte count, x10^9/L*	52.4 (17.4-391)	52 (17.4-391)	71.4 (34-176)	0.64	1 (0.99-1.01)
Percentage immature WBC†	20 (46.5)	17 (44.7)	3 (60)	0.65	1.9 (0.3-12.3)
Monocyte*	2 (0.0-11.0)	2 (0.00-10.0)	4 (1.0-11.0)	0.28	1.2 (0.9-1.6)
Myeloid:erythroid ratio*	9.4 (3.0-92.0)	9.35 (3.0-92.0)	8.5 (3.0-10)	0.4	0.9 (0.7-1.03)
Bone marrow blast	40 (93.0)	3 (7.7)	0	1	NA
Abnormal karyotype	7 (18.4)	7 (20.6)	0 (0.0)	1	NA
Abnormal FISH	2 (5.3)	2 (5.9)	0 (0.0)	1	NA
ASXL1 mutations	25 (60.0)	22 (56.4)	3 (60.0)	1	1 (0.1–13.4)
SETBP1 mutations	14 (35.9)	13 (38.2)	1 (20.0)	0.64	0.4 (0.01-4.8)
SRSF2 mutations	8 (30.8)	8 (33.3)	0 (0.0)	1	NA
Uric acid*	7.9 (2.3-14.4)	7.9 (2.3-14.4)	8 (6.7-9.2)	0.97	0.99 (0.6-1.7)
LDH*	261 (133-1814)	261 (133-1,814)	266 (185-397)	0.61	1 (0.99-1)
Ferritin, ng/mL*	414 (61-12,706)	467 (108-12,706)	273 (61-285)	0.29	1 (0.98-1)

*Presented as median (range); †peripheral blood. CI: confidence interval; FISH: fluorescence *in situ* hybridization; LDH: lactate dehydrogenase; NA: could not be estimated; OR: odds ratio; WBC: white blood cell count.

Although WBC response to ruxolitinib, a JAK inhibitor (JAKi), was observed in 60% of *CSF3R*^{MUT}-CNL patients, this was not superior to hydroxyurea. In a phase II trial that applied more stringent response criteria, 13 (76%) of the 17 patients with *CSF3R*^{MUT}-CNL had partial or complete response to ruxolitinib.[11] Similarly, a phase II study of fedratinib, another JAKi, showed preliminary efficacy in the trial participants, reporting symptom improvement in three of five evaluable patients and associated splenic response in one.[12] It is worth mentioning that the study included patients with MDS/MPN (N=19) and those with CNL (N=5); however, outcomes for the CNL subgroup were not reported separately. The study also reported enriched response in patients with *CSF3R*^{MUT}. In our cohort, one patient received fedratinib combined with hydroxyurea, achieving partial WBC reduction without splenic response, treatment was discontinued after 10 months due to cytopenia. This patient harbored *ASXL1, SETBP1*, and *SRSF2* mutations and did not respond to prior ruxolitinib therapy. Further characterization of the CNL subgroup in the fedratinib study and comparative evaluation of JAK inhibitors would be valuable.

Our study highlights the prognostic weight of having either *ASXL1* or *SETBP1* mutations, which not only predicted worse OS but was also independently associated with BT, Figure 1 and *Online Supplementary Table S2*. One or both of these mutations were present in 75% of patients in this study, supporting previous reports and further revealing the central role of these mutations in disease biology.[2,3] *ASXL1*, an epigenetic modulator, has been shown *in vivo* to synergistically drive myeloid proliferation when co-occurring with *CSF3R*^{MUT}.[13] Similarly, *SETBP1* induces a Myc-driven transcriptional program that promotes leukemogenesis in

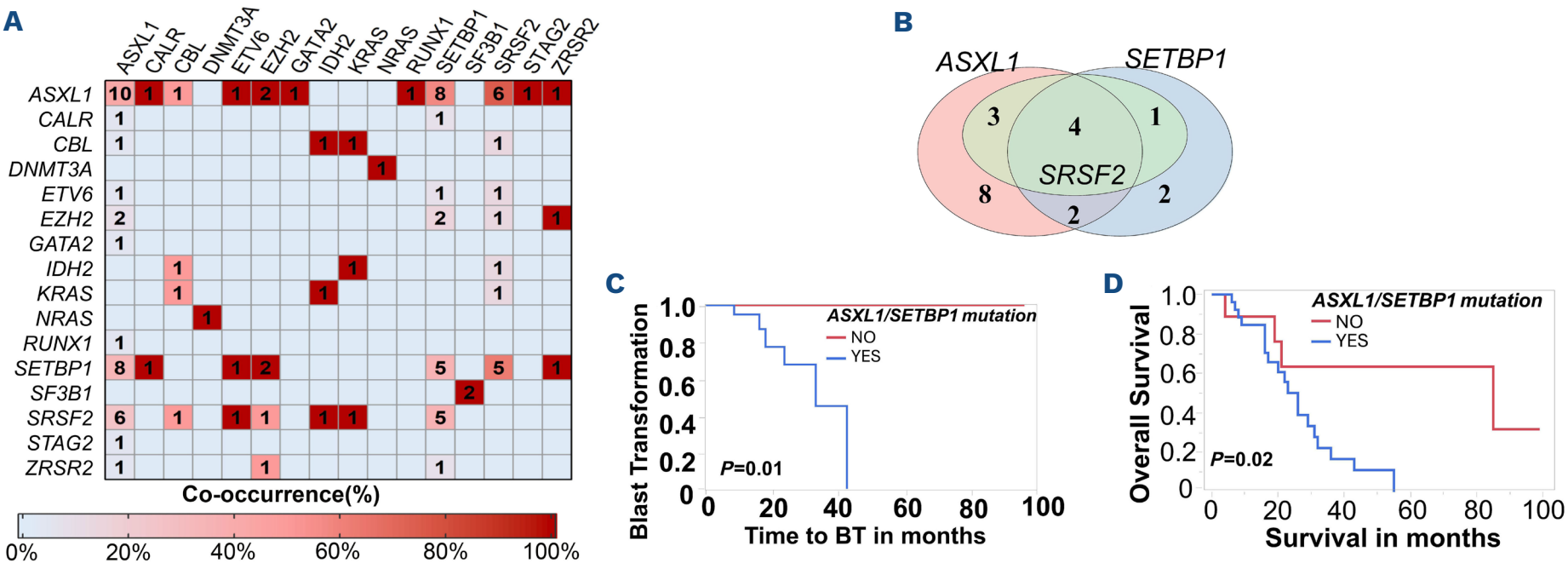


Figure 1. Co-mutations and their prognostic impact in *CSF3R*-mutated chronic neutrophilic leukemia. (A) Heatmap showing co-occurrence of myeloid mutations. *ASXL1, SETBP1,* and *SRSF2* were the most frequent co-mutated genes. The intensity of shading represents the percentage of co-occurrence between gene pairs. (B) Venn diagram illustrating overlap between *ASXL1, SETBP1,* and *SRSF2* mutations. (C) Kaplan-Meier analysis of time to blast transformation (BT). Patients with *ASXL1* or *SETBP1* mutations (blue) had significantly shorter time to transformation (median 35 months, 95% confidence interval [CI]: 19-45) compared to those without these mutations, in whom no transformation was observed within the follow-up period (*P*=0.01). (D) Kaplan-Meier analysis of overall survival. Patients with *ASXL1* or *SETBP1* mutations (blue) had significantly inferior survival (median 26 months; 95% CI: 16-31) compared to patients without these mutations (median 85 months; 95% CI: not reached; *P*=0.02).

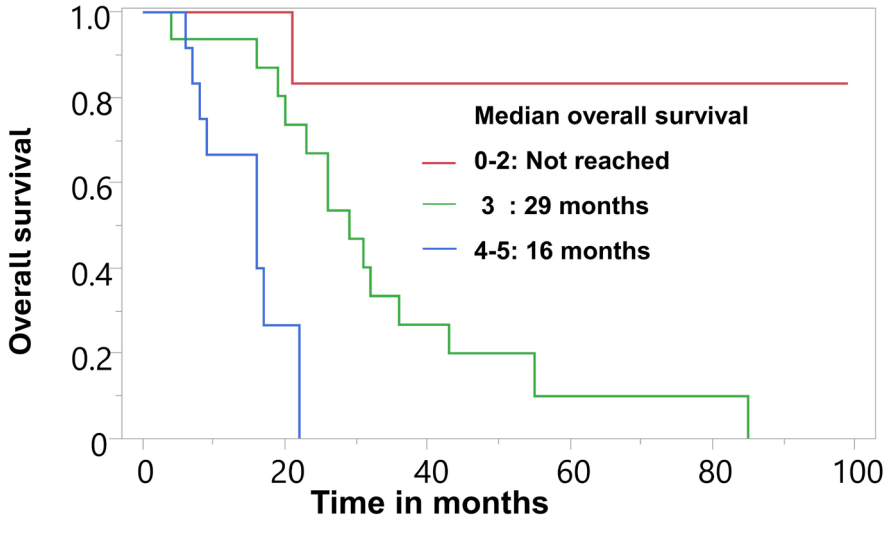


Figure 2. Overall survival according to risk categories. Overall survival stratified by adverse risk score. One adverse point was allocated for age >60 years, and 2 points each for white blood cell count >50×10^9/L and the presence of *ASXL1* or *SETBP1* mutations. Patients were stratified into low-risk (0-2 points), intermediate-risk (3 points), and high-risk (4-5 points) groups, with corresponding median overall survival of not reached, 29 months, and 16 months, respectively (*P*<0.01).

the setting of *CSF3R*^{MUT}.[14] Together, these biological insights reinforce their emerging clinical relevance and these will be more precisely defined as larger patient cohorts are studied.

We reported new clonal abnormalities observed at CNL progression/transformation in *Online Supplementary Table S3*. Notably, new trisomy 21 was observed in three of the 11 patients with available data on clonal evolution, one at BT and two at CNL progression. This finding aligns with a recent report suggesting chromosome 21 amplification, potentially occurring here from copy number gain, may drive BT in myeloproliferative neoplasm through overexpression of *DYRK1A*.[15]

In summary, this study provides a comprehensive description of *CSF3R*^{MUT}-CNL patients, highlighting survival benefits of ASCT in eligible patients and the prognostic impact of *ASXL1*^{MUT}/*SETBP1*^{MUT}, providing a framework for better risk stratification and individualized management.

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Disclosures

NG has served on the advisory board for DISC Medicine and Agios. The other authors have no conflicts of interest to disclose

Contributions

AB and AT designed the study. AB, AT, JCL, and NS collected data. AB and AT performed analyses and wrote the manuscript. AA, AP, AT, MAE, MS, NG, TB, and WJH participated in patient care. CM, KKH, and RH provided hematopathology and molecular laboratory expertise. All authors reviewed the final draft of the manuscript.

Data-sharing statement

Please email the corresponding author for original data.

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