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Two cases of Chronic Neutrophilic Leukemia were successfully treated with Allogeneic Stem Cell Transplantation

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ABSTRACT

Objective: Chronic Neutrophilic Leukemia (CNL) is a rarely seen myeloproliferative neoplasia (MPN) in which the BCR-ABL1 gene mutation is negative, and is characterized by persistent neutrophilic proliferation in the bloodstream and granulocytic hyperplasia in the bone marrow. CNL is usually diagnosed incidentally in asymptomatic individuals with persistent neutrophilic leukocytosis. When genetically examined, BCR-ABL1 fusion gene, JAK-2 V617F, and exon12 mutations, CALR mutations, PDGFRA-B, FGRF1 mutations are all not detected, while CSF3R mutation is observed in most of the cases. The WHO-2016 classification determined the presence of CSF3R T618I and other activating CSF3R mutations as diagnostic criteria. While the prognosis is poor in CNL cases with the CSF3R T618I mutation, it is more moderate in the presence of other CSF3R mutations. The average life expectancy is 21-30 months, and 5-year survival rates are around 28%. Although no treatment modality provides an average survival advantage other than hematopoietic stem cell transplantation (HSCT), there is no accepted 'standard of care' consensus. HSCT procedures performed in CNL cases are limited in the literature.

Case: In this study, we presented two cases of CNL who were successfully treated with allogeneic stem cell transplantation and cured.

Keywords: Neutrophilic Leukemia, Stem cell transplantation

INTRODUCTION

Chronic Neutrophilic Leukemia (CNL), which Tuohy first described in the 1920s, is a very rarely seen myeloproliferative neoplasia (MPN) in which the BCR-ABL1 gene mutation is negative and is characterized by persistent neutrophilic proliferation in the bloodstream and granulocytic hyperplasia in the bone marrow (1). Although it was considered as separate myeloid neoplasia until 2001, it was later included in MPN in the WHO-2001 classification of neoplastic diseases (2, 3). The actual incidence is unknown, the mean age at diagnosis is usually 67 years. The male/female ratio is slightly in favor of males (4).

Clinically, it can be presented in different ways. It is usually diagnosed incidentally in asymptomatic individuals with persistent neutrophilic leukocytosis. Fatigue, bone pain, itching, and easy bleeding/bruising are common constitutional findings. Hepatosplenomegaly is seen in approximately 36% of CNL cases (5). The most important laboratory finding is sustained neutrophilic leukocytosis. While mature neutrophils constitute more than 80% of all leukocytes, blasts and other immature cells are rarely observed in peripheral blood. Although monocytosis and basophilia/eosinophilia are not expected findings, mild anemia and thrombocytopenia may be observed (4).

The leukocyte alkaline phosphatase (LAP) score and LDH levels are increased. Progressive thrombocytopenia and splenomegaly may herald blastic crisis. Bone marrow biopsy usually shows hypercellularity (>80%) and myeloid/erythroid ratio >20:1 in bone marrow aspiration. The absence of dysplastic changes and absence of overt reticulin fibrosis can be considered typical for CNL (4).

When genetically examined, BCR-ABL1 fusion gene, JAK-2 V617F, exon12 mutations, CALR mutations, PDGFRA-B, and FGRF1 mutations are not detected, while CSF3R mutation is observed in most of the cases (6). The WHO-2016 classification determined the presence of CSF3R T618I and other activating CSF3R mutations as diagnostic criteria (6, 7). CNL diagnostic criteria are shown in **Table-1**.

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Table 1.WHO diagnostic criteria of Chronic Neutrophilic Leukemia

Peripheral Blood	Leukocytosis ≥25x10^9
	Segmented plus band forms ≥80% of WBC
	Neutrophil precursors < 10% of WBC
	Myeloblast rarely observed
	Monocyte count < 1x10^9
Bone Marrow	M/E >10
	Normal neutrophil maturation
	Myeloblasts <5% of nucleated cells
Genetic	Presence of CSF3R T618I or other CSF3R mutations
	BCR-ABL1 negativity
	JAK2 V617F negativity
	PDGFRA-B negativity
	FGFR1 negativity

While the prognosis is poor in CNL cases with the CSF3R T618I mutation, it is moderate in the presence of other CSF3R mutations. Overall survival is 21-30 months and 5-year survival rates are around 28% (8, 9). Blastic transformation is observed in 10-21.2% (10, 11) of the cases in the literature, while the meantime for transformation is 21 months (12, 13). Although there is no widely accepted prognostic scoring system, platelets lower than 160x10^9 /L, leukocytes more than 60x109/L, and the presence of ASXL1 mutation are accepted as poor prognostic criteria (1).

Although no treatment modality provides an average survival advantage other than hematopoietic stem cell transplantation (HSCT), there is no accepted 'standard of care' consensus. Hydroxyurea is the most common agent used in the first line to reduce leukocytosis and splenomegaly (4). IFN-alpha, hypomethylating agents, ruxolitinib, thalidomide, cladribine, and imatinib are other treatment alternatives that can be considered in cases where hydroxyurea is not successful. HSCT procedures performed in CNL cases are limited in the literature. For the first time, HSCT was performed on two CNL cases by Hasle et al in 1996 and long-term remission was achieved. While poor results are obtained in the HSCT procedure performed in CNL cases in the blastic phase, satisfactory results can be obtained if it is performed in the chronic phase (4, 13). The 1-year median survival after HSCT has been reported to be 40%. CSF3R can be considered as a minimal residual disease marker, and CSF3R follow-up is recommended after HSCT (14). Considering the very few case reports and studies in the literature, it is recommended that especially high-risk CNL cases be referred to HSCT at the most appropriate period.

CASE 1

A 30-year-old female patient was referred to the hematology outpatient clinic due to leukocytosis, which was noticed during a routine check-up in 2016. The only clinical finding detected in the asymptomatic patient was splenomegaly (longitudinal length 19 cm, passing below the ribs). Laboratory findings of the patient are given in **Table-2**. t(9;22) was not detected by FISH. JAK2 V617F, CALR, and MPL mutations were also not observed. While leukocytosis consisting of mature neutrophils was observed in the peripheral smear, no cells were found in the blast morphology. Bone marrow biopsy revealed hypercellularity (>95% cellularity), M/E ratio of 15:1, myeloblast <5%, and mild reticulin fibrosis. Whole-genome sequencing was performed with next-generation sequencing analysis, pThr618IIe CSF3R gene mutation was detected. The patient was diagnosed with CNL and hydroxyurea was started. No clinical or laboratory improvement was observed in the patient who used hydroxyurea for approximately 14 months. In February 2018, by using a myeloablative conditioning regimen, HSCT was applied from her sister, who was fully compatible with HLA (10/10). The patient, whose chimerism rate on the 100th day after transplantation was 98% compatible with donor lymphocytes, is still being followed in the hematology clinic in a healthy and untreated condition.

CASE 2

A 33-year-old female patient applied to the dentist in January 2020. After the detection of neutrophilic leukocytosis in the examinations, the patient was started on a 2-week course of antibiotics. Despite the treatment, the patient's leukocyte count increased, she was consulted to the hematology department. She had splenomegaly in the physical examination and had a leukoerythroblastic blood smear. Chronic myeloid leukemia (CML) was considered at the forefront, and evaluation of t(9;22) by FISH was planned from peripheral blood, and a bone marrow biopsy was performed. FISH for t(9;22) was negative. The bone marrow biopsy result was compatible with myeloproliferative neoplasia without fibrosis. JAK2 V617F mutation, CALR, MPL, PDGFRA-B, and FGRF1 mutations were found negative, in the myeloid mutation panel examined with NGS, heterozygous mutation in the 13th exon of the ASXL1 rs373221034 gene, and on the 14th and 17th exon of CSF3R gene (c2326 and c1853) were detected. The patient who was diagnosed with CNL did not benefit from the hydroxyurea and the WBC count reached 65x109/L in the follow-up. Since she did not have an HLA-matched sibling donor, HSCT was performed from an unrelated donor who had 9/10 HLA compatibility with a myeloablative conditioning regimen in November 2020. No CSF3R mutation was detected for minimal residual disease screening at the fifth month after HSCT. The patient is followed up in a healthy and untreated way in the first year after allogeneic stem cell transplantation.

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Table 2. Laboratory and clinical findings of the patients

	Patient 1	Patient 2
WBC	$26x10^9$/L	$36x10^9$/L
Absolute neutrophil count	$24x10^9$/L	$31.7x10^9$/L
Hb	14.9 g/dL	11.7 g/dL
Platelet	$122X10^3$/L	$258x10^3$/UL
LDH	365 U/L	1269 U/L
Blast (peripheral blood)	No blast	1 blast
Splenomegaly	18 cm	19 cm
JAK2 V617F	-	-
BCR-ABL1	-	-
CALR	-	-
MPL	-	-
PDGFRA-B	-	-
FGRF1	-	-
CSF3R T618I	+	-
CSF3R other mutations	-	+
ASXL1	-	+
M/E (bone marrow)	15	8
Reticulin fibrosis	0	+1 (mild)

DISCUSSION

CNL is an MPN whose laboratory features have been known for many years, but the treatment algorithm has not been fully clarified. Although the prognosis is heterogeneous, it is known that it has an aggressive course, especially in cases carrying the ASXL1 mutation together with the CSF3R T618I mutation.

Although the ASXL1 mutation was positive in one of the cases we presented, if it was thought to be associated with the CSF3R c2326 mutation and the other case had a CSF3R T618I mutation without the ASXL1 mutation, the cases could be placed in the intermediate-risk class. Since both cases were young and had compatible stem cell donors, they were accepted as candidates for HSCT. Similar to the literature, the patients we presented are followed in a healthy and untreated way after allogeneic stem cell transplantation.

CONCLUSION

In CNL cases, HSCT is the only curative treatment modality that should be considered at the earliest time, especially if the patient is young and has the performance to cope with complications that may develop after allogeneic stem cells.

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