Successful Allogeneic Stem Cell Transplantation with Ruxolitinib Maintenance Therapy for *CSF3R T618I* Mutant Chronic Neutrophilic Leukemia

CSF3R T618I Mutant Kronik Nötrofilik Lösemide Ruksolitinib İdame Tedavisi ile Başarılı Allojeneik Kök Hücre Nakli

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To the Editor,

Chronic neutrophilic leukemia (CNL) is a rare potentially aggressive myeloproliferative neoplasm with oncogenic driver mutations in the colony-stimulating factor 3 receptor (CSF3R) found in approximately 83% of cases [1]. Allogeneic stem cell transplantation (allo-SCT) is the only curative CNL treatment but survival depends on early referral [2] and the rate of transplant-related mortality is high [3]. We report a patient with CNL involving the *CSF3R T618I* mutation who had complete remission (CR) after allo-SCT with ruxolitinib maintenance therapy.

A 48-year-old woman with recurrent purpura on the extremities for over 1 month was admitted in November 2018. She had splenic enlargement 2 cm below the left costal margin, decreased platelets ($17x10^9$/L), and increased white blood cell (WBC) count ($51.6x10^9$/L), neutrophils (81.9%), and hemoglobin (118 g/L). Circulating immature WBCs (promyelocytes 6%, myelocytes 1%) were present. A bone marrow (BM) examination showed myeloproliferation with increased myeloid cells (6.5:1). The myeloblast ratio was 4.5%. BM biopsy revealed granulocytic hyperplasia and decreased megakaryocytes. Karyotyping revealed 46,XX[20]. Fluorescence in situ hybridization excluded *BCR-ABL1*, *PDGFRA*, and *PDGFRB* rearrangements. Targeted next-generation sequencing showed *CSF3R T618I* and *GATA2* mutations and a biallelic *CEBPA* mutation. The Mayo prognostic model suggested a high-risk case.

Before the transplant, the HCT-Comorbidity Index score was 0 and the performance status score was 1. A myeloablative Bu/Cy conditioning regimen was instituted, followed by allo-SCT using donor blood progenitor cells from a sibling donor in December 2018 without pre-transplant treatment. Graft-versus-host disease (GVHD) prophylaxis included cyclosporine until month +6, mycophenolate mofetil until myeloid engraftment, and short-term methotrexate. On day +32, BM showed 98.71% donor chimerism and the *T618I*, *CEBPA*, and *GATA2* mutations were absent in BM aspirates. Maintenance therapy started on day +35 with ruxolitinib at 5 mg twice daily until month +24 and then once daily in months +24 and +25. There were no grade 3-4 hematological adverse events (Figure 1) or non-hematological adverse events including GVHD. At month +43, the patient remained in CR.

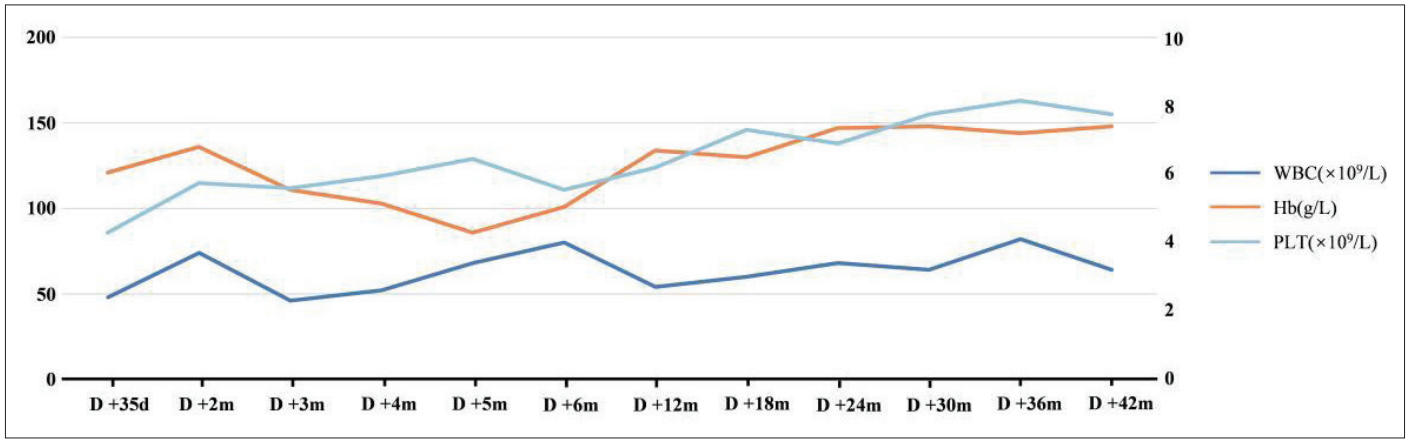

Figure 1. Hematological parameters of the patient after treatment with ruxolitinib.

WBC: White blood cell count; Hb: hemoglobin; PLT: platelet count; D: day; d: days; m: months.

Ruxolitinib inhibits activation of *JAK1/2* and the *CSF3R T618I* mutation, decreasing autonomous cell proliferation in CNL [2,4]. Numerous studies support the use of ruxolitinib in cases of *CSF3R T618I* mutations [2,4,5], but the efficacy of ruxolitinib maintenance therapy is unknown when *CSF3R-T618I* is negative after a transplant. We concluded that ruxolitinib could be an effective maintenance drug based on two previously reported cases of patients with CNL involving *CSF3R T618I* mutation with remission after ruxolitinib treatment, and these patients continued to take ruxolitinib to remain in remission even after the *CSF3R T618I* mutation was no longer detectable [5]. The optimal dose in cases of CNL is uncertain but daily administration of 10-30 mg appears reasonable [5]. As BM tolerance may decrease after a transplant, we used a dose of 5 mg twice daily for maintenance. The optimal maintenance duration is also undetermined. In vivo modeling and clinical studies suggest that ruxolitinib offers a potential approach for GVHD prevention while preserving the graft-versus-tumor effect [5,6,7]; approximately 60% of patients develop at least one episode of chronic GVHD within 2 years of transplant [8]. The data presented here imply that 24 months of ruxolitinib maintenance therapy may reduce chronic GVHD recurrence.

This study is encouraging compared to previous findings of CNL patients receiving allografts without ruxolitinib maintenance therapy [9]. However, a large-scale study is still needed to verify whether allo-SCT is the predominant factor here or not.

Keywords: Chronic neutrophilic leukemia, *CSF3R T618I*, Ruxolitinib, Allogenic stem cell transplantation

Anahtar Sözcükler: Kronik nötrofilik lösemi, *CSF3R T618I*, Ruxolitinib, Allojeneik kök hücre nakli

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Ethics

Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of the relevant institution.

Authorship Contributions

Concept: P.Y., Q.L., M.J., X.G., Y.L.; Design: P.Y., Q.L., M.J., X.G., Y.L.; Data Collection or Processing: P.Y., Q.L., M.J., X.G., Y.L.; Analysis or Interpretation: P.Y., Q.L., M.J., X.G., Y.L.; Literature Search: P.Y., Q.L., M.J., X.G., Y.L.; Writing: P.Y., Q.L., M.J., X.G., Y.L.

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