T618I-Mutated Colony Stimulating Factor 3 Receptor in Chronic Neutrophilic Leukemia and Chronic Myelomonocytic Leukemia Patients who Underwent Allogeneic Stem Cell Transplantation

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Dear Editor

Recently, the mutations within the colony-stimulating factor 3 receptor gene (CSF3R) have been reported as a specific marker of chronic neutrophilic leukemia (CNL) and atypical CML (aCML) [1, 2]. The current WHO system classifies CNL as a BCR-ABL1-negative myeloproliferative neoplasm (MPN). However, in routine clinical practice, it is difficult to clearly distinguish CNL from aCML, chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia, and MDS/MPN, unclassifiable under the MDS/MPN umbrella [3]. Therefore, molecular characteristics (e.g., CSF3R mutation) need to be included in the WHO diagnostic criteria. Here, we describe two CSF3R T618I-mutated patients with CNL and CMML, respectively, who underwent allogeneic stem cell transplantation (allo-SCT).

A 40-yr-old man presented in 2012 with marked neutrophilia. His total white blood cell count was 77.24 × 10^9/L with a differential of 80% neutrophils, 3% band forms, 3% metamyelocytes, 1% myelocytes, 1% promyelocytes, 1% blasts, 3% lymphocytes, and 10% monocytes (Fig. 1A). He had a 23-cm splenomegaly. His bone marrow (BM) aspirate and biopsy showed hypercellularity with granulocytic hyperplasia (Fig. 1B), with a normal karyotype and no evidence of BCR-ABL1, PDGFRα, or PDGFRB rearrangement when examined by FISH. Molecular studies demonstrated the absence of JAK2 V617F and BCR-ABL1 transcripts. CNL was diagnosed in accordance with the WHO diagnostic criteria, and the patient was treated with hydroxyurea. However, his neutrophilia persisted in the peripheral blood as anemia and thrombocytopenia developed. Repeated BM examinations showed hypercellular BM with granulocytic hyperplasia and decreased megakaryocytes, and a clonal chromosomal abnormality of 46,XY,der(18;21)(q10;q10),+21[7]/47,+21[5]/46 ,XY[8]. The CSF3R T618I mutation was detected (Fig. 2A). He then underwent myeloablative allo-SCT, using cells from an unrelated donor. At day 35 following the allo-SCT, BM examination showed 70% cellularity with 100% donor chimerism. The T618I mutation was not detected in the BM aspirates through sequencing (Fig. 2C).

A 60-yr-old man who presented with recurrent purpura on his extremities was referred to our hospital. He had constitutional symptoms including fatigue and weight loss. A computed tomography scan of the abdomen showed splenomegaly. His total white blood cell count was 77.24 × 10^9/L with a differential of 80% neutrophils, 3% band forms, 3% metamyelocytes, 1% myelocytes, 1% promyelocytes, 1% blasts, 3% lymphocytes, and 10% monocytes (Fig. 1A). He had a 23-cm splenomegaly. His bone marrow (BM) aspirate and biopsy showed hypercellularity with granulocytic hyperplasia (Fig. 1B), with a normal karyotype and no evidence of BCR-ABL1, PDGFRα, or PDGFRB rearrangement when examined by FISH. Molecular studies demonstrated the absence of JAK2 V617F and BCR-ABL1 transcripts. CNL was diagnosed in accordance with the WHO diagnostic criteria, and the patient was treated with hydroxyurea. However, his neutrophilia persisted in the peripheral blood as anemia and thrombocytopenia developed. Repeated BM examinations showed hypercellular BM with granulocytic hyperplasia and decreased megakaryocytes, and a clonal chromosomal abnormality of 46,XY,der(18;21)(q10;q10),+21[7]/47,+21[5]/46 ,XY[8]. The CSF3R T618I mutation was detected (Fig. 2A). He then underwent myeloablative allo-SCT, using cells from an unrelated donor. At day 35 following the allo-SCT, BM examination showed 70% cellularity with 100% donor chimerism. The T618I mutation was not detected in the BM aspirates through sequencing (Fig. 2C).

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A raphy scan of the abdomen demonstrated 13.5-cm mild splenomegaly. His peripheral blood (Fig. 1C) and BM findings (Fig. 1D) were consistent with CMML-1. The patient had a normal karyotype with no evidence of BCR-ABL1, PDGFRA, or PDGFRB rearrangement following FISH examinations. Molecular studies demonstrated the absence of JAK2 V617F and BCR-ABL1 transcripts. The CSF3R T618I mutation was identified through direct sequencing (Fig. 2B). An initial azacitidine treatment failed to achieve any response. Thus, he underwent allo-SCT using cells from a sibling donor. At day 30 following the allo-SCT, a BM examination showed 30% cellularity with 97% donor chimerism. The CSF3R T618I mutation was not detected in the BM aspirates (Fig. 2D).

Since high-frequency of CSF3R mutations in CNL (89%) and, to a lesser extent, in aCML (40%) were discovered [1, 4], Pardanani et al. [2] has confirmed that the CSF3R T618I mutation was detected exclusively in cases of WHO-defined CNL, with a mutational frequency of 83%. Thus, CSF3R T618I mutation should be a diagnostic criterion for CNL.

Previous studies showed discordant frequencies in the CSF3R mutations in CMML and aCML. Maxson et al. [1] reported that eight of 20 aCML (40%) cases exhibited CSF3R mutations, whereas Pardanani et al. [2] did not find the CSF3R mutation in any case of aCML. Although CSF3R mutations have been observed in 4% of patients with CMML, they are distinct from membrane proximal mutations; the T618I mutation was identi-
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CSF3R mutation in CNL and CMML

Fig. 2. Sequencing of genomic DNA isolated from peripheral blood leukocytes, demonstrating the CSF3R c.1853C>T (p.Thr618Ile) mutation. The CSF3R T618I mutation was detected in patient #1 with CNL, pre-allo-SCT (A) and in patient #2 with CMML at diagnosis (B). After allo-SCT, the mutation was not detected in patient #1 (C) and in patient #2 (D).

Abbreviations: CNL, chronic neutrophilic leukemia; allo-SCT, allogeneic stem cell transplantation; CMML, chronic myelomonocytic leukemia.

In a majority of patients with CNL [5], however, we observed one CMML patient harboring the CSF3R T618I mutation. To incorporate CSF3R mutations into the diagnostic criteria of these disorders, the frequency, the location, and the specificity of the CSF3R mutations need to be determined.

Although there is no current standard of care for CNL or for aCML, allo-SCT may be applicable to young patients with potential for blast transformation and progressive refractory neutrophilia [6-9]. In our two CNL and CMML patients harboring the CSF3R T618I mutation, and who had undergone allo-SCT, the CSF3R T618I mutation was not detected following allo-SCT.

This suggests a predictive role of this mutation in post-transplant relapse, supported by prior studies showing a correlation between post-transplant relapse and the persistence of the CSF3R T618I in aCML [10]. Thus, testing for the CSF3R mutation may lead to genetically informed therapy and useful diagnostic approach. The influence of the CSF3R mutations on genotype-phenotype associations, disease prognosis, and the efficacy of the therapeutic inhibition of CSF3R-related signaling needs to be clarified.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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