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LETTER TO THE EDITOR

Molecular response of *CSF3R* T618I harboring chronic neutrophilic leukemia after induction chemotherapy linked to cord blood transplantation

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Dear editor,

Chronic neutrophilic leukemia (CNL) is a rare type of myeloproliferative neoplasm (MPN) which is characterized by the activation mutation of the colony-stimulating factor 3 receptor (*CSF3R*) [1]. Due to the rarity of the disease, a standard treatment algorithm of CNL is not established. Here, we present a CNL patient harboring the *CSF3R* T618I mutation who achieved a molecular response after conventional chemotherapy and subsequently received a cord blood transplantation.

A 52-year-old Japanese woman was referred to our institute with lumbago. The complete blood count tests showed increased white blood cell (WBC) counts (135.78×10^9/L, neutrophils 62.5%) and decreased platelet counts (PLT 34×10^9/L). Immature WBCs (promyelocytes 2.5%, myelocytes 0.5%, metamyelocytes 5.5%, and myeloblasts 16%) appeared in the peripheral blood. Bone marrow examination revealed hypercellularity with increased myeloid series (myeloid to erythroid ratio, 17:1) (Fig. 1d). The ratio of myeloblasts was 8% (Fig. 1g). Fluorescence in situ hybridization (FISH) revealed that the patient did not have *BCR-ABL*, *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangements. G-banded karyotyping showed 47, XX, +22 [1/20]/46, XX [19/20]. After approval from the institutional review board, informed written consent was obtained from the patient, and DNA was extracted from the bone marrow mononuclear cells. Molecular analysis of the CSF3R gene was performed as described by Maxson et al. [2]. We found the *CSF3R* T618I mutation (Fig. 1a); however, *JAK2* V617F, *CALR* exon9, and *MPL* mutations were not detected. We diagnosed the patient as having an accelerated phase of CNL. We started induction chemotherapy with idarubicin 5 mg/m^2 (3 days) and cytarabine 100 mg/m^2 (7 days). Forty-two days after the initiation of induction chemotherapy, bone marrow examination was performed. The cellularity of bone marrow decreased to normal levels, and the ratio of immature blasts dropped to 2% (Fig. 1e, h). Importantly, analysis of the *CSF3R* T618I mutation revealed a more than 90% decrease in abnormal clones (Fig. 1b). After one cycle of high-dose cytarabine therapy (HD-AC) as consolidation, we performed allogeneic hematopoietic stem cell transplantation (allo-HSCT) with cord blood. A bone marrow examination at 97 days after transplantation showed normocellular marrow (Fig. 1f) and no abnormal increase in immature bone marrow cells (Fig. 1i). Additionally, the *CSF3R* T618I mutation was not detected in bone marrow cells (Fig. 1c). At present, 9 months after transplantation, the patient has sustained complete remission and complete donor hematopoietic chimerism.

The most important finding of the present case is showing the usefulness of conventional chemotherapy for the treatment of transformed-phase CNL. In addition to morphologically reducing blast cells, a molecular analysis confirmed the reduction of clones harboring the *CSF3R* T618I mutation after treatment with idarubicin and cytarabine. Molecular response of CNL patients has been reported by two groups; however, these patients

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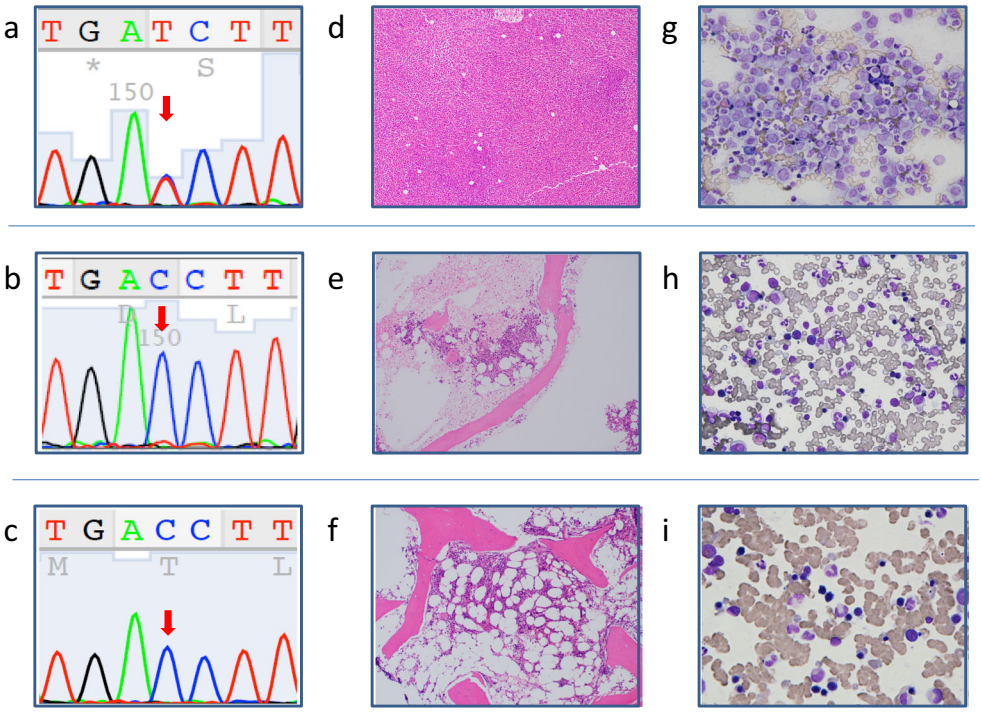

Fig. 1 Changes in the *CSF3R* T618I mutation levels (**a**, **b**, and **c**), bone marrow cellularity (**d**, **e**, and **f**), and ratio of myeloblasts in bone marrow (**g**, **h**, and **i**). (**a**, **d**, **g**) At initial diagnosis. (**b**, **e**, **h**) After induction chemotherapy. (**c**, **f**, **i**) After allo-HSCT. Red arrows in **a**, **b**, and **c** indicate the C-to-T mutation that resulted in the *CSF3R* T618I mutation

achieved remission after allo-HSCT [3, 4]. To our knowledge, this is the first case report of CNL that achieved molecular response after conventional chemotherapy.

Our experience suggested that conventional chemotherapy might be a useful option to achieve remission linking to allo-HSCT.

Compliance with ethical standards Informed consent was obtained from the patient for the treatment. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

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