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Kim-Hien T. Dao, Oregon Health and Science University
Magdolna B. Solti, Compass Oncology
Julia E. Maxson, Oregon Health and Science University
Elliott Winton, Emory University
Richard D. Press, Oregon Health and Science University
Brian J. Druker, Oregon Health and Science University
Jeffrey W. Tyner, Oregon Health and Science University

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Significant clinical response to JAK1/2 inhibition in a patient with CSF3R-T618I-positive atypical chronic myeloid leukemia

Kim-Hien T. Dao\textsuperscript{a,1}, Magdolina B. Solti\textsuperscript{b}, Julia E. Maxson\textsuperscript{a}, Elliott F. Winton\textsuperscript{c}, Richard D. Press\textsuperscript{d}, Brian J. Druker\textsuperscript{a,e}, Jeffrey W. Tyner\textsuperscript{a,f}

\textsuperscript{a} Oregon Health and Sciences University, Knight Cancer Institute, Hematology and Medical Oncology, Portland, OR, USA
\textsuperscript{b} Emory University, Winship Cancer Institute, Atlanta, GA, USA
\textsuperscript{c} Oregon Health and Sciences University, Department of Pathology, Portland, OR, USA
\textsuperscript{d} Howard Hughes Medical Institute, Oregon Health and Sciences University, Portland, OR, USA
\textsuperscript{e} Oregon Health and Sciences University, Knight Cancer Institute, Cell and Developmental Biology, Portland, OR, USA
\textsuperscript{f} Oregon Health and Sciences University, Knight Cancer Institute, Hematology and Medical Oncology, Portland, OR, USA

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\textbf{A B S T R A C T}

Mutations in CSF3R (colony-stimulating factor 3 receptor) are frequent oncogenic drivers in chronic neutrophilic leukemia (CNL) and atypical chronic myeloid leukemia (aCML). Here we describe a 75 year old man who was diagnosed with CSF3R-T618I-positive atypical CML. He presented with leukocytosis, anemia, and thrombocytopenia and developed massive splenomegaly and severe constitutional symptoms. Hydroxyurea was given over a 6 month period but failed to provide any measureable clinical benefit. Eventually, he was treated with ruxolitinib, an FDA-approved JAK1/2 inhibitor, which resulted in dramatic improvement of his blood counts. He also had significant reduction of spleen volume and constitutional symptoms. This case highlights the need for a clinical trial to interrogate JAK1/2 as a potential molecular target in CNL and aCML in patients with or without CSF3R mutation. A clinical trial evaluating the safety and efficacy of ruxolitinib for this patient population is registered at ClinicalTrials.gov (NCT02092324).

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1. Introduction

Clinically, CNL and aCML are rare leukemias characterized by varying degrees of leukocytosis, anemia, thrombocytopenia, splenomegaly, and constitutional symptoms. Key distinguishing pathologic features between CNL and aCML are summarized in Table 1 [1]. No standard of care is established for CNL and aCML and the reported median overall survival is approximately two years [2]. Recently, Maxson, et al. reported CSF3R mutations in ~90% of patients with CNL and in ~40% of patients with aCML [3]. Subsequent studies confirmed this high frequency of CSF3R mutation in CNL while observing a lower frequency in aCML [4]. Mutations in CSF3R generally occur in the extracellular membrane proximal domain or result in premature truncation of the cytoplasmic tail. Of note, membrane proximal mutations are far more common [3]. These membrane proximal mutations cause significant activation of JAK/STAT signaling. Therefore, targeting of the JAK/STAT pathway may inhibit granulocytic proliferation and provide clinical benefit to patients with CNL or aCML. Ruxolitinib (Incyte Corporation) is the first FDA-approved JAK1/JAK2 inhibitor with a reported IC50 of 3.3 nM and 2.8 nM, respectively [5]. In preclinical studies, targeting JAK1/2 with ruxolitinib significantly suppressed CSF3R-T618I-induced malignant colony growth compared to no drug treatment controls [6]. Transplantation of T618I-CSF3R-expressing mouse bone marrow cells was sufficient to produce a highly penetrant, lethal neutrophilic leukemia in a mouse model. Treatment of experimental mice with ruxolitinib provided disease control and improved survival compared to untreated controls [6]. These studies suggest that targeting JAK1/2 may provide clinical benefit to patients with these rare types of leukemia.

2. Case study

A 75 year old man with Parkinson’s disease was diagnosed with aCML in April 2013 based on pathologic review of his bone marrow biopsy and on the finding of the CSF3R-T618I mutation. According to old records, leukocytosis (not otherwise specified) was present as far back as 2005. His CBC before he began taking hydroxyurea showed WBC 71.3 x 10\(^{9}\)/microliter, ANC 42.1 x 10\(^{9}\)/microliter, Hgb 9.8 g/dL, MCV 98.3 fl, and platelet 97 x 10\(^{11}\)/microliter. His peripheral blood
showed 12% immature granulocytes and hypogrannular neutrophils and rare pseudo-Pelger–Huet neutrophils. His bone marrow showed granulocytic hyperplasia (myeloid:erythroid ratio > 15:1) and hypo-lobulated megakaryocytes in 30% of megakaryocytes. Peripheral and marrow blasts were less than 1%. In addition to the CSF3R-T618I mutation (50% allele frequency), his disease also harbored CBL-I383T (70% allele frequency) and KDM6A-S114C (100% allele frequency on one X chromosome) mutations evaluated by massively parallel sequencing. SETBP1 was wildtype. His disease was characterized by progressive leukocytosis, anemia, thrombocytopenia, splenomegaly, and constitutional symptoms. Performance status was ECOG of 3. Physical exam revealed a chronically ill-appearing, cachectic male with splenomegaly. His bone marrow had reduced granulocytic hyperplasia and rare pseudo-Pelger

<table>
<thead>
<tr>
<th>Blood</th>
<th>Chronic neutrophil leukemia</th>
<th>Atypical chronic myeloid leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immature granulocytes</td>
<td>&lt; 10%</td>
<td>≥ 10%</td>
</tr>
<tr>
<td>Myeloblasts</td>
<td>&lt; 1%</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>Marrow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocytic hyperplasia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Myeloblasts</td>
<td>≤ 5%</td>
<td>≤ 20%</td>
</tr>
<tr>
<td>Granulocytic dysplasia</td>
<td>Minimal/absent</td>
<td>Present</td>
</tr>
<tr>
<td>Megakaryocytic dysplasia</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

* Promyelocytes, myelocytes, and metamyelocytes.

In summary, this case highlights the potential clinical benefit of JAK1/2 inhibition for patients with CNL or aCML with CSF3R mutations in patients with CNL and aCML in a prospective clinical trial is needed to establish the (1) frequency of clinical responses, (2) durability and depth of clinical responses, (3) genetic modifiers of disease characteristics and clinical responses such as co-existing SETBP1 or TET2 mutations, and (4) impact on long-term quality of life and overall survival. As of this report, a prospective, multi-center phase II clinical trial investigating the safety and efficacy of ruxolitinib in this patient population is registered at ClinicalTrials.gov (NCT02092324) and is open for participant recruitment.

In summary, this case highlights the potential clinical benefit of JAK1/2 inhibition for patients with CNL or aCML with CSF3R mutations. It is not known yet whether patients with wildtype CSF3R will experience the same clinical benefit. Many patients with CNL and aCML present with severe anemia and thrombocytopenia thus limiting the usefulness of hydroxyurea. The recent discovery of frequent mutations in CSF3R in patients with CNL and aCML and the preclinical studies supporting JAK1/2 as a molecular target have uncovered a potential line of therapy for these rare types of leukemia associated with very poor prognosis.

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References


Fig. 1. Clinical response in a patient with CSF3R-T618I-positive aCML treated with ruxolitinib. (A) WBC, platelet, Hgb, and MCV laboratory values during ruxolitinib treatment. Refer to case study description for details. Hydroxyurea was stopped at the indicated red circle and ruxolitinib was started at 10 mg twice daily at the indicated green triangle, both on the x-axis. Subsequent green triangles indicate when ruxolitinib was increased to 15 mg twice daily, then to 20 mg twice daily. (B) Spleen volume was determined by conventional prolate ellipsoid method (0.524 × W × T × ML; width, thickness, and max length). Two different ultrasound views are shown, the transverse and longitudinal views. Before ruxolitinib treatment, the spleen was diffusely echogenic with hyperechoic nodules. The spleen measured 25.6 × 19.5 × 16.6 cm; volume = 4342 cm³. After 3 months of ruxolitinib treatment, the spleen was normal in echogenicity and the hyperechoic nodules resolved. The spleen measured 18.5 × 14.3 × 7.6 cm; volume = 1053 cm³. (C) Shown is the MPN-SAF symptom questionnaire as filled out by the patient. The total symptom score (the sum of each line) is quantitative and a useful tool to monitor symptoms and treatment responses [7]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)