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

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

Journal Title: Leukemia Research Reports
Volume: Volume 3, Number 2
Publisher: Elsevier: Creative Commons | 2014-08-01, Pages 67-69
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1016/j.lrr.2014.07.002
Permanent URL: https://pid.emory.edu/ark:/25593/s2d5v

Final published version: http://dx.doi.org/10.1016/j.lrr.2014.07.002

Copyright information:
© 2014 The Authors
This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommerical-NoDerivs 3.0 Unported License (http://creativecommons.org/licenses/by-nc-nd/3.0/).

Accessed September 22, 2020 7:59 PM EDT
Case report

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

Kim-Hien T. Dao\textsuperscript{a,*}, Magdolna 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} Emory University, Winship Cancer Institute, Atlanta, GA, USA

\textsuperscript{*} Correspondence to: Oregon Health and Sciences University, Knight Cancer Institute, 3181 SW Sam Jackson Park Road, UHN73C, Portland, OR 97239, USA.
Tel.: +1 503 494 7894; fax: +1 503 494 3688.
E-mail address: 5Tdao@ohsu.edu5T (K.-H. Dao).

ARTICLE INFO

Article history:
Received 10 May 2014
Accepted 12 July 2014
Available online 1 August 2014

Keywords:
Colony-stimulating factor 3 receptor
Chronic neutrophilic leukemia
Atypical chronic myeloid leukemia
Ruxolitinib

ABSTRACT

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).

\copyright 2014 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

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 \textasciitilde 90% of patients with CNL and in \textasciitilde 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 7.13 \times 10^{9}/microliter, ANC 42.1 \times 10^{9}/microliter, Hgb 9.8 g/dL, MCV 98.3 fl, and platelet 97 \times 10^{12}/microliter. His peripheral blood
showed 12% immature granulocytes and hypogranular neutrophils and rare pseudo-Pelger–Huet neutrophils. His bone marrow showed granulocytic hyperplasia (myeloid:erythroid ratio > 15:1) and hypolobulated 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 profound weight loss, pancytopenia, and constitutional symptoms. He began taking hydroxyurea in April 2013 at 28 mg/kg per day. His dose was increased to 15 mg/kg twice a day on day 0 and to 20 mg/kg twice a day on day 84. He was tapered off hydroxyurea and was completely off on day 14. As shown in Fig. 1A, the WBC and MCV were reduced gradually over 3 months while his Hgb and platelets steadily increased, indicating improved marrow function by targeting JAK1/2 inhibition of JAK kinases rather than other kinase targets uninvolved in the sanctuary of the bone marrow microenvironment. It will be important to expand upon prior work to confidently show that specific inhibition of JAK kinases rather than other kinase targets underlie these clinical responses. The safety profile and clinical benefit 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 novel therapeutic approach to treating CNL/aCML.

### Table 1

| Blood                        | Chronic neutrophil leukemia | Atypical chronic myeloid leukemia |
|------------------------------|-----------------------------|----------------------------------|
| Immature granulocytes        | < 10%                        | >10%                             |
| Myeloblasts                  | < 1%                         | >20%                             |
| Marrow                       |                             |                                  |
| Granulocytic hyperplasia     | Present                      | Present                          |
| Myeloblasts                  | < 5%                         | >20%                             |
| Granulocytic dysplasia       | Minimal/absent               | Present                          |
| Megakaryocytic dysplasia     | Absent                       | Present                          |

---

On December 2013 the patient was started on ruxolitinib 10 mg twice a day (day 0). His dose was increased to 15 mg twice a day on day 57 and to 20 mg twice a day on day 84. He was tapered off hydroxyurea and was completely off on day 14. As shown in Fig. 1A, the WBC and MCV were reduced gradually over 3 months while his Hgb and platelets steadily increased, indicating improved marrow function by targeting JAK1/2 signaling and going off hydroxyurea. His peripheral blood showed reduced immature granulocytes while the neutrophils displayed increased cytoplasmic granularity/toxic granulation. His bone marrow had reduced granulocytic hyperplasia (myeloid:erythroid ratio 10:1) and fewer hypolobulated megakaryocytes compared with the pre-ruxolitinib bone marrow evaluation. Peripheral and marrow blasts were less than 1%. In addition, his spleen volume was reduced by approximately 75% after approximately 4 months of ruxolitinib treatment. Single colony assays confirmed that the allele frequency was not significantly reduced.

### 3. Discussion

Here we report a case of CSF3R-T618I-positive aCML with a robust clinical response to JAK1/2 inhibition with ruxolitinib. The clinical benefit in this case was not merely leukoreduction but also improved marrow function as evident by near normalization of Hgb, MCV, and platelet counts. In addition, the patient had a significant reduction in spleen volume and constitutional symptoms, which were refractory to hydroxyurea. In the report by Maxson et al. [3] a clinical case of CSF3R-T618I-positive CNL was described where the patient also had plateaued and Hgb improvement with ruxolitinib. These clinical cases suggest interesting differences between myelofibrosis (primary, post-polycythemia vera, and post-essential thrombocytosis) and CNL/aCML. As noted in the Comfort I study, a randomized placebo-controlled phase III clinical trial with ruxolitinib in patients with myelofibrosis, (1) thrombocytopenia is a dose-limiting toxicity, (2) WBC is not substantially reduced in myelofibrosis patients, and (3) marrow function is not measureably improved with ruxolitinib despite clinical responses (spleen and symptom reduction). One similarity is that the allele burden of the oncogenic driver is not significantly reduced with ruxolitinib [8].

The case described here suggests that targeting JAK1/2 in CNL/aCML may provide clinical benefit beyond spleen and symptom reduction, and may suppress the malignant clone and enhance normal hematopoiesis more effectively than that seen in myelofibrosis. Interestingly, we did not detect a reduction in CSF3R-T618I allele frequency or overall bone marrow cellularity after 3 months of treatment, suggesting that JAK1/2 inhibition may preferentially affect cells not in the sanctuary of the bone marrow microenvironment. It will be important to expand upon prior work to confidently show that specific inhibition of JAK kinases rather than other kinase targets underlie these clinical responses. The safety profile and clinical benefit of ruxolitinib treatment or other JAK1/2 inhibitors 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.

### Acknowledgments

K.-H.T. Dao et al. / Leukemia Research Reports 3 (2014) 67–69

K.T.D. received support from the OHSU Knight Cancer Institute and the National Institutes of Health, National Heart, Lung and Blood...
References

[1] The International Agency for Research on Cancer. In: Swerdlow S, Campo E, Lee Harris N, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue (IARC WHO Classification of Tumours). 4th ed.. World Health Organization; 2008. p. 441.

[2] Gotlib J, Maxson JE, George TI, Tyner JW. The new genetics of chronic neutrophilic leukemia and atypical CML: implications for diagnosis and treatment. Blood 2013;122(10):1767–11.

[3] Maxson JE, Gotlib J, Poliyea DA, Fleischman AG, Agarwal A, Eide CA, et al. Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. N Engl J Med 2013;368(10):1781–90.

[4] Pardanani A, Lasho TL, Laborde RR, Elliott M, Hanson CA, Knudson RA, et al. CSF3R T618I is a highly prevalent and specific mutation in chronic neutrophilic leukemia. Leukemia 2013;27(9):1870–3.

[5] Mascarenhas J, Hoffman R. Ruxolitinib: the first FDA approved therapy for the treatment of myelofibrosis. Clin Cancer Res 2012;18(11):3008–14.

[6] Fleischman AG, Maxson JE, Luty SB, Agarwal A, Royer LR, Abel ML, et al. The CSF3R T618I mutation causes a lethal neutrophilic neoplasia in mice that is responsive to therapeutic JAK inhibition. Blood 2013;122(22):3628–31.

[7] Emanuel RM, Dueck AC, Geyer HL, Kiladjian JJ, Slot S, Zweegman S, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol 2012;30(33):4098–103.

[8] Emanuel RM, Dueck AC, Geyer HL, Kiladjian JJ, Slot S, Zweegman S, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol 2012;30(33):4098–103.