Insights from a rare myeloproliferative neoplasm with coexisting BCR-ABL1 fusion gene, CALR and TET2 mutations treated with nilotinib and ruxolitinib

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Abstract

Myeloproliferative neoplasms (MPNs) with concurrent BCR-ABL1 fusion gene and CALR mutation are especially rare. We report a patient with coexisting BCR-ABL1 fusion gene, CALR and TET2 mutations who was treated with the combination of the second-generation TKI nilotinib and JAK1/JAK2 inhibitor ruxolitinib.

Case report Title: Insights from a rare myeloproliferative neoplasm with coexisting *BCR-ABL1* fusion gene, *CALR* and *TET2* mutations treated with nilotinib and ruxolitinib **Short title:** MPN with coexisting *BCR-ABL1*, *CALR* and *TET2* mutations **Authors:** Li Huo^{1*}, Jundan Xie^{1*}, Qian Wang^{1*}, Hongjie Shen¹, Zixuan Ding¹, Lijun Wen¹, Zhao Zeng¹, Yi Xu¹, Changgeng Ruan^{1,2}, Suning Chen^{1,2#}, Mengxing Xue^{1#}

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CASE REPORT

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Abstract

Myeloproliferative neoplasms (MPNs) with concurrent *BCR-ABL1* fusion gene and *CALR* mutation are especially rare. The clonal relationship between two disorders and other genetic events that might contribute to the cooccurrence of more than one type of MPN in a patient are uncertain. Moreover, the safety and efficacy of the combination of tyrosine kinase inhibitor (TKI) and *JAK1/JAK2* inhibitor for these patients is still unclear. We report a patient with coexisting *BCR-ABL1* fusion gene, *CALR* and *TET2* mutations who was treated with the combination of the second-generation TKI nilotinib and *JAK1/JAK2* inhibitor ruxolitinib. The *CALR* -mutant, *TET2* -mutant, *BCR-ABL1* -positive subclone disappeared immediately after nilotinib treatment, while the *CALR* -mutant, *TET2* -mutant, *BCR-ABL1* -negative subclone and the initial dominant *CALR* -mutant, *TET2* -wild, *BCR-ABL1* -negative clone persisted even after treatment with a combination of nilotinib and ruxolitinib. The *CALR* -mutant, *BCR-ABL1* -positive subclone sensitive to nilotinib may arise from the initial dominant *CALR* -mutant, *BCR-ABL1* -negative clone, which was resistant to nilotinib. The combination treatment with TKI and ruxolitinib was safe and effective in MPNs with concurrent *BCR-ABL1* fusion gene and *CALR* mutation.

Keywords

Myeloproliferative neoplasms, *BCR-ABL1* fusion gene, *CALR* mutation, nilotinib, ruxolitinib

Introduction

Myeloproliferative neoplasms (MPNs) are divided into two categories: chronic myeloid leukemia (CML) characterized by the presence of the *BCR-ABL1* fusion gene and *BCR-ABL1* -negative MPNs. Somatic mutations in Janus kinase 2 (*JAK2*)-V617F, exon 10 of thrombopoietin receptor/myeloproliferative leukemia (*MPL*) or exon 9 of calreticulin (*CALR*) are found in >90% of patients with classical *BCR-ABL1* -negative MPNs[1]. *BCR-ABL1* fusion gene and *JAK2/MPL/CALR* mutations are usually considered to be mutually exclusive[2]. However, several recent case reports have described patients with coexisting *BCR-ABL1* fusion gene and *JAK2/MPL/CALR* mutations[3-5]. Among these isolated cases, patients with concurrent *BCR-ABL1* fusion gene and *CALR* mutation are especially rare. The clonal relationship between two disorders and other genetic events that might contribute to the cooccurrence of more than one type of MPN in a patient are uncertain. Moreover, the safety and efficacy of the combination of tyrosine kinase inhibitor (TKI) and *JAK1/JAK2* inhibitor for these patients are still unclear. Here, we report a patient with coexisting *BCR-ABL1* fusion gene, *CALR* and ten-eleven translocation oncogene family member 2 (*TET2*) mutations who was treated with the combination of the second-generation TKI nilotinib and *JAK1/JAK2* inhibitor ruxolitinib.

Case report

In December 2014, a 42-year-old female presented to our hospital with massive splenomegaly (9 cm below the costal margin). The initial complete blood count analysis showed a white blood cell count of $165 \times 10^9/L$, a hemoglobin (Hb) level of 68 g/L, and a platelet count of $156 \times 10^9/L$. Bone marrow aspiration showed marked granulocytic proliferation with an increased myeloid:erythroid ratio. Cytogenetic analysis revealed t(9;22)(q34;q11) in 10 out of 10 metaphase cells, and fluorescence in situ hybridization (FISH) for *BCR-ABL1* was also positive (93%). Reverse transcriptase polymerase chain reaction (RT-PCR) confirmed a *BCR-ABL1* fusion gene, and the *BCR-ABL1* transcript level, which was shown as the ratio of *BCR-ABL1* to *ABL1* on an international scale (*BCR-ABL1* IS), was 17.035% by quantitative RT-PCR (qRT-PCR). Thus, the patient was diagnosed with chronic-phase CML and was initially treated with hydroxyurea, which caused a rapid reduction in the leucocyte count to a normal level. A week later, hydroxyurea was substituted with nilotinib at a dosage of 600 mg/day. Although splenomegaly and anemia persisted (6 cm below the costal margin and Hb: 87 g/L after one year of nilotinib treatment), the patient achieved a complete cytogenetic response (CCyR) after 3 months of nilotinib treatment and achieved a major molecular response 12 months later (Figure 1A). In December 2016, the patient arrived at our hospital with appetite loss, fatigue and increased splenomegaly (7 cm below the costal margin). Cytogenetic analysis demonstrated a CCyR, while *BCR-ABL* IS was 0.06% by qRT-PCR. The bone marrow biopsy showed granulocytic and erythrocytic hyperplasia accompanied by

reticulin fibrosis grade 3. Molecular studies detected a 34-bp deletion in *CALR* exon 9 (c.1103-1136del, K368fs*51) (Figure 1B), which was also observed in a previous study¹, with a variant allele frequency (VAF) of 51.3% in the absence of *JAK2* V617F and *MPL* mutations. Retrospective analysis of historical samples showed that the *CALR* mutation had been present since the initial diagnosis of CML with a stable allele burden regardless of the decrease of *BCR-ABL1* IS (Figure 1A). To investigate other genetic mutations that might contribute to this rare event of the concurrent *BCR-ABL1* fusion gene and *CALR* mutation, we also retrospectively studied the mutational status of 51 genes (Supplementary Table S1) that are usually mutated in hematologic malignancies by next-generation sequencing. A mutation in *TET2* (c. 3748G>T, p. E1250Ter) (Figure 1B) was detected in all historical samples analyzed, and the VAFs were slightly lower than that of the *CALR* mutation (Figure 1A). Ruxolitinib was administered at a dosage of 10 mg twice daily with the continuation of nilotinib, when the patient's constitutional symptoms worsened with progressive splenomegaly (8 cm below the costal margin) in June 2017. After 6 months of combination therapy, which the patient tolerated well, there was significant improvement of the constitutional symptoms and reduction in splenomegaly (6 cm below the costal margin). At the last follow-up at our hospital in December 2018, the patient continued the combination treatment with nilotinib and ruxolitinib and maintained the original doses. Her constitutional symptoms had disappeared, while the spleen size remained 6 cm below the costal margin. Within 18 months of combination therapy, the VAF of *CALR* mutation fluctuated from 45.7% to 46.5%, and *BCR-ABL1* IS decreased to 0.01% (Figure 1A). Since 2019, this patient returned to the local hospital for treatment. As the telephone follow-up in October 2020, she continued the combination treatment, splenomegaly and anemia still existed, *BCR-ABL1* IS was lower than 0.01%, *CALR* mutation and *TET2* mutation were not analyzed.

Results and discussion To the best of our knowledge, there have been 21 patients with coexisting *BCR-ABL1* fusion gene and the *CALR* mutation reported in the literature, including our patient (Table 1). Only two of these patients had both the *BCR-ABL1* fusion gene and *CALR* mutation identified simultaneously at initial diagnosis (Table 1). Five of the seven patients with initial diagnosis of *BCR-ABL1* -negative MPN had no detectable *BCR-ABL1* fusion gene and/or Ph+ chromosome at initial diagnosis and then acquired this molecular alteration at a later time with a median time to the second diagnosis of 48 months (range, 30-336 months); the other 2 patients had no available data (Table 1). Otherwise, 9/12 patients with initial diagnosis of *BCR-ABL1* -positive CML had not only the *BCR-ABL1* fusion gene but also the *CALR* mutation by retrospective analysis of initial samples at the first diagnosis, and 3 patients did not undergo retrospective analysis of the *CALR* mutation (Table 1). These isolated cases suggested that the *CALR* mutation usually occurred earlier than the *BCR-ABL1* fusion gene. As observed in other case reports^[2,6,7], in our patient, the mutant *CALR* retained a high VAF of 45.7%-53.8%, while the *BCR-ABL1* IS decreased to 0.01% after nilotinib treatment. Therefore, we speculate that the *CALR* -mutant, *BCR-ABL1* -positive subclone sensitive to nilotinib arose from the initial dominant *CALR* -mutant, *BCR-ABL1* -negative clone, which was resistant to nilotinib (Figure 1C-D). Additionally, we also detected the *TET2* mutation in our patient, which was found in 10% to 20% of all MPN subtype^[8]. At initial diagnosis, the VAF of *TET2* mutation was 47.5%; together with the VAF of the *CALR* mutation (51.3%) and the *BCR-ABL1* -positive cells determined by FISH (93%), this suggests that the *CALR* mutation, *TET2* mutation and *BCR-ABL1* fusion gene coexisted in nearly all cells at this time. As the *BCR-ABL1* IS decreased to 0.597% after 3 months of nilotinib treatment, the VAF of the *TET2* mutation also decreased to 32.8% and was maintained at a similar level, which was lower than that of the *CALR* mutation (Figure 1A). This result suggested that the *BCR-ABL1* -positive subclone arose from the *CALR* -mutant, *TET2* -mutant clone, and the *TET2* mutation might have occurred after *CALR* mutation (Figure 1C-D). A previous study^[9], which found that patients in whom the *JAK2* mutation was acquired first presented at a younger age than patients in whom the *TET2* mutation was acquired first (60.71 years vs. 71.17 years), also supported our hypothesis, as our patient was only 42 years old at initial diagnosis. The clinical and morphologic appearance of our case at initial presentation was more suggestive of a diagnosis of CML, despite the coexistence of *BCR-ABL1* and *CALR* mutation. With the decrease of *BCR-ABL1* IS subsequent to nilotinib therapy, the patient showed constitutional symptoms, increased splenomegaly and myelofibrosis, which suggested the presence of a *CALR* mutation and supported the diagnosis of primary myelofibrosis (MF). This finding suggested that the clinical and morphologic features

of patients with coexisting *BCR-ABL1* and *CALR* mutation might be dominated by *BCR-ABL1*, which was also observed in previous reports[6,7]. Given the overlapping clinical and morphologic features of MPN, it is important to test all of the mutations in *JAK2/MPL/CALR* and the *BCR-ABL1* status in patients suspected of having MPNs.

As observed in CML patients[10] and patients with coexistent *BCR-ABL1* and *JAK2* mutation[11], combination treatment with TKI and ruxolitinib in our patient was safe and effective, which was also confirmed by three previous patients with coexistent *BCR-ABL1* and *CALR* mutation, one treated with imatinib/dassatinib and ruxolitinib[3] and the others with imatinib and ruxolitinib[4,5]. Moreover, recent studies found that the combination of ruxolitinib and nilotinib had a synergistic effect against both CML stem cells[12] and MF cells[13], so our combination of nilotinib and ruxolitinib may have been better for this patient. However, the *CALR* mutation allele burden was not decreased and the splenomegaly persisted after 18 months of ruxolitinib therapy. Other choices should be considered for this patient. Interferon- α was reported to induce molecular responses in *CALR*-mutated essential thrombocythemia, but not for the patients with additional nondriver mutations (including *TET2* mutation)[14]. Allogeneic stem cell transplant, if eligible for this procedure, may be a superior option. Due to the scarcity of cases, the optimal treatment modality for patients with coexisting *BCR-ABL1* and *JAK2/MPL/CALR* mutations remains uncertain, and a multicenter study with a large patient population may help address this unknown issue.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethics statement

This study was approved by the Ethics committee of the First Affiliated Hospital of Soochow University.

Consent

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Author contributions

L.H. and M.X.X. wrote the manuscript; S.N.C, L.H. and M.X.X. were involved in the clinical management of the reported patient; M.X.X., H.L., J.D.X, and Q.W. interpreted data and created figures; J.D.X., H.J.S, Z.X.D, L.J.W., Z.Z. and Y.X. assisted with methods; Q.W., C.G.R. and S.N.C contributed to the revisions of the manuscript.

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Figure legend

Figure 1. (A) Spleen size, hematological, cytogenetic and molecular data acquired during the follow-up of this patient with myeloproliferative neoplasm with coexisting *BCR-ABL1* fusion gene, *CALR* and *TET2* mutations. *BCR-ABL1* transcript levels are shown as the ratio of *BCR-ABL1* to *ABL1*, expressed as a percentage on the international scale (*BCR-ABL1* -IS). The *CALR* and *TET2* mutations were detected by next-generation sequencing and confirmed by Sanger sequencing. *CALR* mutation monitoring was performed using polymerase chain reaction followed by capillary electrophoresis. The variant allele frequency (VAF) of the *CALR* mutation was calculated by dividing the mutant peak area by the sum of the mutant and wild-type peak areas. *TET2* mutation monitoring was performed using next-generation sequencing. (B) Sanger sequencing of *CALR* confirmed a frameshift mutation (c.1103_1136del, p.K368fs*51). Fragment length analysis by capillary electrophoresis showed concurrent amplification of the wild-type allele and a mutant allele. Sanger sequencing of *TET2* confirmed a nonsense mutation (c.3748G>T, p.E1259Ter). (C) Clonal evolution from the first diagnosis of CML to the last follow-up. Mutant burdens were estimated according to the percentage of *BCR-ABL1* -positive cells by FISH and the VAF of *CALR/TET2* mutations. Fish plot^[15] showed that the *CALR* -mutant, *TET2* -mutant, *BCR-ABL1* -positive subclone disappeared immediately after nilotinib treatment, while the *CALR* -mutant, *TET2* -mutant, *BCR-ABL1* -negative subclone and the initial dominant *CALR* -mutant, *TET2* -wild, *BCR-ABL1* -negative clone persisted even after treatment with a combination of nilotinib and ruxolitinib. (D) Schematic diagram of speculative clonal architecture and the order of alteration acquisition in this MPN patient.

WBC, white blood cell; Hb, hemoglobin; PLT, platelet; *, below the costal margin.

Dec-14, first diagnosis of CML; Mar-15, 3 months of nilotinib treatment; Dec-16, diagnosis of primary myelofibrosis; Dec-18, 18 months of combination therapy with nilotinib and ruxolitinib.

Figure 1

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