Case Report

Efficacy of ruxolitinib in a patient with myelodysplastic/myeloproliferative neoplasm unclassifiable and co-mutated JAK2, SF3B1 and TP53

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ABSTRACT

Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U) is a rare but heterogeneous subtype of MDS/MPN, with no specific genetic alterations and standard treatments. ASXL1, SRSF2, TET2, JAK2 and NRAS are commonly mutated in MDS/MPN-U. Double gene mutations could be detected in MDS/MPN-U, however, co-mutations of 3 and more genes in this disease entity are very rare. Here, we present a case of MDS/MPN-U with triple mutations involving JAK2, SF3B1, and TP53. After failure of traditional therapy including hydroxyurea and interferon-α, the patient received ruxolitinib monotherapy and achieved hematological response quickly. Though mutations in TP53 implied a poor prognosis in myeloid malignancies, this patient has maintained no AML transformation for 26 months since diagnosis. Further research on complex mutations in the pathogenesis and prognosis of MDS/MPN-U is warranted.

1. Introduction

The "unclassifiable" myelodysplastic/myeloproliferative neoplasm (MDS/MPN-U) is a rare subtype of MDS/MPN, which accounts for less than 5% of all myeloid disorders [1]. Based on the previous single-institution and retrospective studies, MDS/MPN-U has unique phenotypes and genetic aberrations [2], such as JAK-STAT pathway activation and low frequency of TET2 mutation. JAK2 V617F has been detected in 25% of MDS/MPN-U patients, which is most frequently co-mutated with SRSF2 [3]. Mutations of SF3B1 have been reported in 12% of MDS/MPN-U patients. Co-mutations of JAK2 V617F with SF3B1 have been detected in 63.8% of MDS/MPN-RS-T patients and correlated with elevated sideroblasts in the bone marrow [4]. Mutations of TP53 have been detected in 8% of such patients, correlating with rapid AML transformation and poor prognosis [5]. To our knowledge, there are no reported MDS/MPN-U cases with triple mutations involving JAK2, SF3B1 and TP53 simultaneously.

It has been reported that patients with MDS/MPN-U have a poor prognosis with a median overall survival of only 12 to 24 months based on traditional therapies such as hydroxyurea and interferon, which call for clinical trials in this disease entity [6]. Though JAK2 V617F accounts for about 12% of MDS/MPN-U patients, clinical trials of JAK-STAT inhibitors in this entity are very rare. Here, we present a case of MDS/MPN-U treated by ruxolitinib, who has co-mutations of JAK2, SF3B1 and TP53.

2. Case report

In August 2018, a 57-year-old male was referred to our hospital for the evaluation of leukocytosis and erythrocytosis which had been occasionally detected by routine examination since 2017. He had anorexia and weight loss. Physical examination showed flushing and splenomegaly (with the spleen tip being 38 mm below the left costal margin at the midclavicularline). The peripheral blood count showed: white blood cell (WBC) counts 15.44 × 109/L; red blood cell counts 7.17 × 1012/L; Hemoglobin (Hb) 19.5 g/dL; hematocrit 60.5% and platelets 245 × 109/L. Differentiation of WBC showed 77% of neutrophils, 15% of lymphocytes, 3% of eosinophils, 2% of basophils, 2% of monocytes and 1% of

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1 Statement of equal author’s contribution: Qian Wang and Hai-ping Dai contribute equally to this manuscript.

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myelocytes. Elevated erythropoietin was detected. The bone marrow (BM) aspirate was hypercellular, with myeloid versus erythroid ratio equals to 2.70. 0.5% of blasts and 8% of ring sideroblasts (RS) were detected in the BM (Fig. 1A and B), with no signs of dysplastic in granulocytic and megakaryocytic lineages. The trephine biopsy was also hypercellular (90% of cellularity) with proliferation in all of the myeloid lineages. Reticulin fibrosis (MF-1) was observed. The megakaryocytes frequently formed dense clusters, adjacent to the bone marrow vascular sinuses and bone trabeculae, which are different from that in essential thrombocythemia (Fig. 1C). Cytogenetic analysis revealed a normal karyotype. Rearrangements involving PDGFRA, PDGFRB, FGFR1 and PCM1-JAK2 were all negative by multiplex PCR. Next-generation sequencing (NGS) using a targeted 51-gene panel on BM samples revealed somatic mutations including JAK2 V617F (variant allele frequency, VAF, 90.3%), SF3B1 K666N (VAF, 40.5%), and TP53 R181H (VAF, 3.9%) (Fig. 1D-F). A diagnosis of MDS/MPN-U was made according to the WHO (2016) classification. Based on the R-IPSS scoring system, this patient was classified as very low risk. A score of 30 was got according to the Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF). Hydroxyurea was administered for two weeks, which
was subsequently substituted with IFN-α-2b (Peking Kawin Biotechnology, Beijing, China) at a dose of 3000,000 units, every other day, due to lack of decrease of WBC and Hb.

Three weeks after the initiation of interferon-α–2b treatment, counts of WBC and Hb gradually decreased to the upper limit of normal value. However, enlarged spleen (64 mm below the left costal margin at the midclavicular line, supplementary figure 1) and elevated LDH were detected at the 7-months follow-up, which implied disease progression. Thus a second BM aspiration was performed, which was hypercellular with 1.5% of blasts and 21% of RS. Dysplasia in granulocytes and erythrocytes were observed. BM biopsy was hypercellular (90% of cellularity) with significantly increased and dysplastic megakaryocytes. Reticulin fibrosis progressed to grade MF-2. JAK2 V617F (VAF, 80.75%) was detected by Q-PCR. Sanger sequencing revealed SF3B1K666N but no mutations of TP53 (Fig. 2A and B). MPN-SAF score was still 30 after reassessment. Then IFN-α–2b was replaced by ruxolitinib (10 mg, twice a day). At the 1 month follow-up after ruxolitinib treatment, the size of spleen shrank to 32 mm below the left costal margin at the midclavicular line. At the same time, blood routine test showed a decrease of Hb to 14.5 g/dL, hematocrit to 43.9% and WBC to 10.1 × 10^9/L. Four months later, in October 2019, the spleen shrank to 22 mm below the left costal margin at the midclavicular line and the Hb level decreased to 13.6 g/dL (Fig. 2C and D). No adverse events related to ruxolitinib were observed. MPN-SAF score decreased from 30 at baseline to 4 at the 17-months follow-up after ruxolitinib treatment. This study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University, and informed consent was taken.

3. Discussion and conclusion

Clinical features of MDS/MPN-U are reported to be correlated with the underlying genetic changes. For example, MDS/MPN-U patients with co-mutations of JAK2 and SF3B1 had higher percentage of RS, higher risk of R-IPSS and leukemia transformation [2]. In accordance with this, our patient also had elevated RS (8% at diagnosis and 21% at the 7-months follow-up) in the BM sample. Because this patient had platelet counts of <450 × 10^9/L, the WHO criteria for MDS/MPN-RS-T was not met [7]. According to the literature, MDS/MPN-U patients with >15% BM RS were found to share similar clinical characters and outcomes with MDS/MPN-RS-T in a recent study [2]. Thus, the prognosis of this patient needs to be confirmed with longer follow-up. Approximately 91% of MDS/MPN-U patients had one or more gene mutations [3]. The highest VAF were found in mutant ASXL1 and TET2, followed by JAK2, SRSF2, EZH2, U2AF1 and RUNX1. TP53 mutation was detected in few cases of MDS/MPN-U, which was found to participate in the transformation of MPN into AML and poor prognosis [2,5]. However, minor TP53 mutations were also detected in a significant proportion of MPN patients and reported to have no impact on overall survival [8]. This patient had no signs of AML transformation for 26 months, which might due to the low frequency of TP53 mutation (VAF, 3.9%) at diagnosis. Because only one case was reported in this study, larger studies are necessary to further address prognosis in patients with similar mutational profiles.

Median survival of MDS/MPN-U was short (12.4 to 21.8 months) with traditional treatment [3,6,9]. MDS/MPN-U was also associated with suboptimal responses to hypomethylating drugs and poor OS of only 16.4 months [6]. Ruxolitinib has profound efficacy in MPN with JAK2 mutation in relieving splenomegaly and constitutional symptoms [10]. A phase II trial of ruxolitinib combined with azacitidine had revealed a better median survival in MDS/MPN-U compared to CML and atypical CML [11]. In accordance with the above data, our patient responded well to ruxolitinib. Thus, first-line treatment with ruxolitinib in JAK2mut MDS/MPN-U merits prospective clinical trials.

In general, this report presented a very rare MDS/MPN-U with triple mutations in JAK2, SF3B1 and TP53. Our patient maintained no AML transformation under ruxolitinib monotherapy after failure of traditional therapy, which may suggest that ruxolitinib is a very promising drug in such patients.

Declaration of Competing Interest

All authors have no conflict of interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2020.100229.

References

[1] T.I. Mughal, N.C. Cross, E. Padron, et al., An International MDS/MPN Working Group’s perspective and recommendations on molecular pathogenesis, diagnosis and clinical characterization of myelodysplastic/myeloproliferative neoplasms, Haematologica 100 (9) (2015) 1117–1130.
[2] A.A. Manganakor, D.M. Svoboda, G. Coltro, et al., Clinico-pathologic characteristics, prognostication and treatment outcomes for myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U): mayo Clinic-Moffitt Cancer Center study of 135 consecutive patients, Leukemia 34 (2) (2020) 656–661.
[3] P. Bose, A. Nazha, R.S. Komrokji, et al., Mutational landscape of myelodysplastic/myeloproliferative neoplasm-unclassifiable, Blood 132 (19) (2018) 2100–2103.
[4] J. Jerome, T. Haferlach, V. Grossmann, et al., High frequencies of SF3B1 and JAK2 mutations in refractory anemia with ring sideroblasts associated with marked thrombocytosis strengthen the assignment to the category of myelodysplastic/myeloproliferative neoplasms, Haematologica 98 (2) (2013) e15–e17.
[5] A. Harutyunyan, T. Klampf, M. Gazzola, et al., p53 lesions in leukemia transformation, N Engl J Med 364 (5) (2011) 488–490.
[6] C.D. DiNardo, N. Daver, N. Jain, et al., Myelodysplastic/myeloproliferative neoplasms, unclassifiable (MDS/MPN, U): natural history and clinical outcome by treatment strategy, Leukemia 28 (4) (2014) 958–961.
[7] D.A. Arber, A. Orazi, B. Hasserjian, et al., The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, Blood 127 (20) (2016) 2391–2405.
[8] B. Kubosova, S. Pavlova, J. Malcikova, et al., Low-burden TP53 mutations in chronic phase of myeloproliferative neoplasms: association with age, hydroxyurea administration, disease type and JAK2 mutation status, Leukemia 32 (2) (2018) 450–461.
[9] S.A. Wang, R.P. Hasserjian, P.S. Fox, et al., Atypical chronic myeloid leukemia is clinically distinct from unclassifiable myelodysplastic/myeloproliferative neoplasms, Blood 123 (17) (2014) 2645–2651.
[10] G. Greenfield, S. McPherson, K. Mills, et al., The ruxolitinib effect: understanding how molecular pathogenesis and epigenetic dysregulation impact therapeutic efficacy in myeloproliferative neoplasms, J. Transl. Med. 16 (1) (2018) 360.
[11] R. Ansì, H.M Kantarjian, A phase II trial of ruxolitinib in combination with azacitidine in myelodysplastic syndrome/myeloproliferative neoplasms, Am. J. Hematol. 93 (2) (2018) 277–285.