

Ruxolitinib Plus Decitabine Effectively Treats Myelodysplastic Syndrome/Myeloproliferative Neoplasm, Unclassifiable, by Decreasing the Variant Allele Frequency of *KRAS*

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Abstract: Myelodysplastic syndrome/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U) is a subtype of MDS/MPN that exhibits a combination of the features of both MDS and MPN. To date, no curative treatment is available for MDS/MPN-U; however, previous studies have suggested a potential survival advantage for ruxolitinib and hypomethylating agents. We reported a case of a *JAK2*-negative but *KRAS*-positive MDS/MPN-U patient treated with ruxolitinib plus decitabine. After treatment, the patient's clinical symptoms were moderated, and the size of the spleen and the peripheral blood cell counts were reduced. These effects might be due to the regimen's ability to reduce STAT5 activation and upregulate microRNA-181c to downregulate the variant allele frequency (VAF) of *KRAS*.

Keywords: myelodysplastic syndrome, myeloproliferative neoplasm, decitabine, ruxolitinib, *KRAS*

Introduction

Myelodysplastic syndrome/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U) is a subtype of MDS/MPN that spans from MDS characterized by morphologic dysplasia and ineffective haematopoiesis to MPN with proliferative features.¹ Poor prognosis and without standard treatment facilitated diverse therapeutic studies. Previous studies suggested that hypomethylating agents (HMAs) could improve overall survival (OS) among high-risk MDS/MPN-U.² Moreover, a Phase II trial of ruxolitinib in combination with azacytidine in MDS/MPN demonstrated that the protocol was beneficial to MDS/MPN-U. Here, we found that the decitabine plus ruxolitinib regimen was effective for a *JAK2*-negative but *KRAS*-positive MDS/MPN-U patient.

Patient and Methods

Patient

An 80-year-old female who presented with a greater than 6-month history of dizziness along with fatigue and a 5-month history of leukopenia and anaemia was admitted to our hospital. Excluding penicillin allergy history and amaurosis, she denied a past medical history. Physical examination revealed anaemia appearance and petechial scatter on the palate. Before admission, routine blood tests

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showed that the white blood cell (WBC) count was $3.6 \times 10^9/L$, the haemoglobin (HB) level was 76 g/L, and the platelet (PLT) count was $661 \times 10^9/L$ (Figure 1I). Ultrasonography showed that the spleen was 4.30 cm thick (Figure 1E). A peripheral blood smear revealed 8% blasts with teardrop-shaped red blood cells (Figure 1A). Moreover, the cell morphology of bone marrow (BM) suggested granulocyte hyperplasia along with pathological haematopoiesis (6%), and erythroid lineage hypoplasia revealed only 9% erythroblasts with teardrop-shaped red blood cells. In addition, the number of megakaryocytes decreased with hypersegmentation and multinucleation, whereas the function of megakaryocytes was fine (Figure 1B). Flow cytometry of BM demonstrated that the myeloid progenitor cell percentage was 2.95% and that CD45

expression was increased (Figure 1K). In addition, BM biopsy showed that BM haematopoietic tissue was hyperplastic with immature cell proliferation and morphologic dysplasia as well as slight reticular fibre hyperplasia (Figure 1C and D). Furthermore, *KRAS p. G12D* (34.7%), *EZH2 p. E22Rfs*15* (35.6%), *EZH2 p. N692S* (40.8%), *RUNX1 p. G165Afs*12* (34.6%), *RUNX1 p. D332N* (49.8%), *STAG2 c.2097-2A>G* (30%), *PLCG1 p. A578D* (47.6%), and *CREBBP p. E1050k* (37.3%) were detected by next-generation DNA sequencing (NGS), whereas *JAK2*, *CALR* and *MPL* genes were not (Figure 1J, Tables 1 and 2). Moreover, the chromosome karyotype was normal. The patient harboured cytopenia for 5 months with blasts (8% in peripheral blood smear) and morphologic dysplasia that met the characteristics of MDS.

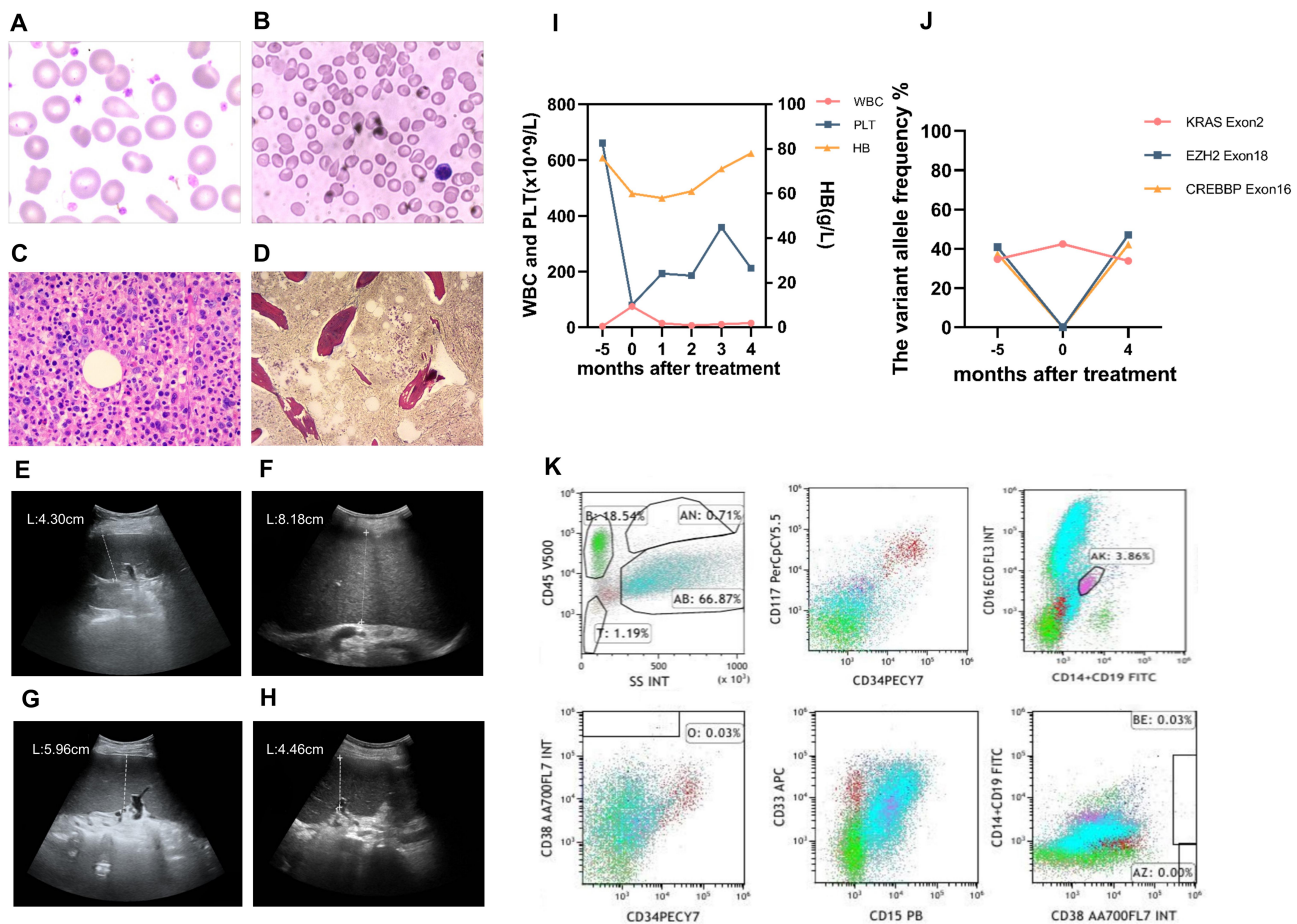


Figure 1 Laboratory and imaging results of patients. (A) Morphological assessment of peripheral blood (Wright's staining, oil-immersion lens, $\times 1000$) revealed teardrop-shaped red blood cells. (B) Morphological assessment of bone marrow (Wright's staining, oil-immersion lens, $\times 1000$) revealed erythroid lineage hypoplasia with teardrop-shaped red blood cells. (C) Bone marrow biopsy (haematoxylin-eosin staining, low power lens, $\times 400$) revealed erythroid lineage hypoplasia. (D) Reticular fibre staining of bone marrow (reticular fibre staining, low power lens, $\times 100$) revealed slight reticular fibre hyperplasia. (E) Splenic ultrasonography revealed that the thickness of the spleen at diagnosis was 4.30 cm. (F) The thickness of the spleen at disease progression was 8.18 cm. (G) The thickness of the spleen at day 15 of the first cycle was 5.96 cm. (H) The thickness of the spleen after 4 cycles of treatment was 4.46 cm. (I) The white blood cell (WBC) count, haemoglobin (HB) level and platelet (PLT) count at diagnosis (5 months before treatment), disease progression (treatment initiation) and after 1 to 4 cycles of treatment (1–4 months after treatment). (J) The variant allele frequency (VAF) of *KRAS* exon 2, *EZH2* exon 18, and *CREBBP* exon 16 mutation at diagnosis (5 months before treatment), disease progression (treatment initiation) and after 4 cycles of treatment (4 months after treatment). (K) The immunophenotype of bone marrow cells revealed increased CD45 expression.

Table 1 Genes Assessed by Targeted Sequencing

1.ABL1	2.ANKRD26	3.ARID1A	4.ASXL1	5.ASXL2	6.ATG2B	7.ATM	8.B2M
9.BCL2	10.BCL6	11.BCOR	12.BCORL1	13.BIRC3	14.BRAF	15.BRINP3	16.BTK
17.CALR	18.CARD11	19.CASP8	20.CBL	21.CCND1	22.CCND2	23.CCND3	24.CCR4
25.CD28	26.CD58	27.CD79B	28.CDC25C	29.CDKN1B	30.CDKN2A	31.CEBPA	32.CNOT3
33.CREBBP	34.CRLF2	35.CSF3R	36.CSNK1A1	37.CUX1	38.CXCR4	39.DDX3X	40.DDX41
41.DIS3	42.DNM2	43.DNMT3A	44.DNMT3B	45.EED	46.ERG1	47.EP300	48.ETNK1
49.ETV6	50.EZH2	51.FAM46C	52.FAT1	53.FBXW7	54.FGFR3	55.FLT3	56.GATA1
57.GATA2	58.GATA3	59.GNAI3	60.ID3	61.IDH1	62.IDH2	63.IKZF1	64.IL7R
65.IRF4	66.JAK1	67.JAK2	68.JAK3	69.KDM6A	70.KIT	71.KLF2	72.KMT2A
73.KMT2D	74.KRAS	75.MAP2K1	76.MAPK1	77.MAX	78.MED12	79.MEF2B	80.MPL
81.MYC	82.MYD88	83.NF1	84.NOTCH1	85.NOTCH2	86.NPM1	87.NRAS	88.NT5C2
89.PAX5	90.PDGFRB	91.PHF6	92.PIGA	93.PLCG1	94.PLCG2	95.PPM1D	96.PRDM1
97.PRKCB	98.PRPS1	99.PTEN	100.PTPN11	101.RAD21	102.RBBP6	103.RELN	104.RHOA
105.RPL10	106.RUNX1	107.SETBP1	108.SETD2	109.SF1	110.SF3B1	111.SH2B3	112.SMC1A
113.SMC3	114.SPEN	115.SRP72	116.SPSF2	117.STAG2	118.STAT3	119.STAT5B	120.SUZ12
121.TAL1	122.TCF3	123.TERT	124.TET2	125.TNFAIP3	126.TNFRSF14	127.TP53	128.TPMT
129.TRAF3	130.U2AF1	131.USP7	132.WHSC1	133.WT1	134.XPO1	135.ZBTB7A	136.ZMYM3
137.ZRSR2	138.NOTCH3	139.NOTCH4	140.PRP8	141.ZNF384			

Table 2 Next-Generation DNA Sequencing of Bone Marrow at Diagnosis

Gene	Mutation Site	Nucleotide	Amino Acid	Db SNP	Rate%
KRAS	Exon2	c.35G>A	p.G12D	rs121913569	34.7
EZH2	Exon2	c.63dupA	p.E22Rfs*15	–	35.6
EZH2	Exon18	c.2075G>A	p.N692S	–	40.8
RUNX1	Exon5	c.492–493dupCG	p.G165Afs*12	–	34.6
RUNX1	Exon9	c.994G>A	p.D332N	–	49.8
STAG2	Intron20	c.2097–2A>G	–	–	30
PLCG1	Exon16	c.1733C>A	p.A578D	–	47.6
CREBBP	Exon16	c.3148G>A	p.E1050k	–	37.3

Abbreviations: SNP, single nucleotide polymorphism; rs, reference single nucleotide polymorphism.

Otherwise, prominent thrombocytosis with BM fibrosis and splenomegaly implied MPN. Furthermore, neither a preceding history of MPN or MDS nor recent cytotoxic or growth factor therapy information was found. *BCR-ABL*, *PDGFR* and *FGFR* fusion in gene analysis or isolated del(5q), chr3 inversion in chromosome or features of mixed MDS/MPN were not revealed. The patient cannot be assigned to MDS, MPN or MDS/MPN other categories; therefore, she was diagnosed with MDS/MPN-U according to the World Health Organization's 2016 version of haematologic neoplasm classification.³

After diagnosis, the patient rejected chemotherapy considering its side effects and was only treated with symptomatic methods. Approximately 5 months later, she complained of decreased appetite and returned to our department. Physical examination showed anaemia, hepatomegaly (one finger under the rib) and splenomegaly (two

fingers under the rib and right edge over midline). The thickness of the spleen was 8.80 cm, whereas the previous thickness was 4.30 cm by ultrasonography (Figure 1F). Shockingly, blood examination revealed that the WBC count was $75.1 \times 10^9/L$, the HB level was 60 g/L, and the PLT count was $80 \times 10^9/L$ (Figure 1I). BM cell morphology displayed extremely increased proliferation of the granulocyte lineage, whereas proliferation of other lineages was inhibited. The myeloid progenitor cell count was 3.60%, which was accompanied by CD117 overexpression and decreased CD45 expression as determined by flow cytometry of BM. BM biopsy illuminated that BM haematopoietic tissue exhibited increasing hyperplasia, and hyperplasia was most prominent in the granulocyte lineage. NGS showed that the variant allele fractions of *KRAS*, *EZH2*, *RUNX1*, *STAG2*, and *PLCG2* mutations were increased (Figure 1J, Table 2).

These manifestations and examinations implied that the disease progressed, so we tried a new regimen that combined ruxolitinib and decitabine. She received 15 mg/m² decitabine intravenously weekly four times for each 28-day cycle and 5 mg ruxolitinib orally twice a day continuously in cycles. The dose of ruxolitinib was adjusted according to the condition, and the maximum dose was 15 mg orally twice a day.

Methods

Genomic DNA was purified from bone marrow with Gentra Puregene Blood Kit (Qiagen, Hil- den, Germany) according to the protocol. High-throughput gene sequencing was performed using ultrahigh multiple PCR exon enrichment technology with an average sequencing depth of 800×. Mutation analysis was performed using the Ion Reporter System and Variant Reporter Software.

Ethics Statement

This study was approved by the Ethics Committee of the Fourth Affiliated Hospital of Zhejiang University School of Medicine. Before collecting clinical isolates from the patient, we informed her of our research purposes, and written informed consent for participation in the study was obtained. Written informed consent for publication of the case details and clinical images was obtained from the patient.

Results

On day 15 of the first cycle, hepatobiliary pancreaticosplenic ultrasonography was performed with a reduced spleen thickness of 5.96 cm (Figure 1G). The uncomfortable symptoms were alleviated, and the WBC count was 14.3×10⁹/L after one cycle. After three cycles, the thickness of the spleen was reduced to 4.80 cm. After four cycles, she felt better. Blood examination revealed that the WBC count was 15.3×10⁹/L, the HB level was 78 g/L, and the PLT count was 212×10⁹/L (Figure 1I). In addition, the thickness of the spleen was decreased to 4.46 cm (Figure 1H). The variant allele frequency (VAF) of *KRAS*, *EZH2*, *RUNXI*, *STAG2* and *PLCG1* mutations was decreased (Figure 1J, Table 3). During the course of disease, no abnormal karyotypes were found. According to the MDS/MPN proposed response criteria for MDS/MPN published by the MDS/MPN International Working Group in 2015,⁴ clinical benefit was obtained.

Safety was assessed based on Common Terminology Criteria for Adverse Events version 4.0. During the

Table 3 The Variant Allele Fraction of Mutations Throughout the Disease Course

Gene	Mutation Site	Rate at Diagnosis %	Rate at Disease Progression %	Rate After Treatment %
<i>KRAS</i>	Exon2	34.7	42.4	33.8
<i>EZH2</i>	Exon2	35.6	48.1	43.5
<i>EZH2</i>	Exon18	40.8	Negative	47.1
<i>RUNXI</i>	Exon5	34.6	49	43.5
<i>RUNXI</i>	Exon9	49.8	47	49.3
<i>STAG2</i>	Intron20	30	35.3	29.1
<i>PLCG1</i>	Exon16	47.6	51.1	47.6
<i>CREBBP</i>	Exon16	37.3	Negative	42.1

treatment, neither haematological toxicity nor nonhaematological toxicity occurred, and all the doses were conducted as planned.

Discussion

MDS/MPN, an overlap disorder, may have mutational profiles that differentiate this condition from analogous disorders.⁵ This disorder is more likely to harbour gene mutations in epigenetic regulators or splicing factors that are related to morphologic dysplasia in conjunction with mutations associated with the activation of growth factor signalling pathways.⁵ Meggendorfer M demonstrated that MDS/MPN-U tended to be associated with mutations in epigenetic regulation, the JAK-STAT pathway and splicing but marginally carried RAS pathway-associated mutations.⁶ In addition, RAS pathway mutations often coexist with *RUNXI*, *GATA2*, and *STAG2* mutations.⁷ The patient harboured *KRAS*, *EZH2*, *RUNXI*, *STAG2*, *PLCG1* and *CREBBP* mutations that were combined epigenetic regulator, transcription factor, and growth factor signalling pathway-associated mutations.

MDS/MPN-U is a disease that exhibits both dysplastic and proliferative features, and accurate risk stratification is undetermined.¹ To date, the prognostic model of MDS/MPN-U refers to MDS or MPN, such as the International Prognostic Scoring System (IPSS) or Revised IPSS (R-IPSS). Previous studies suggested four established MDS prognostic models, which included IPSS,⁸ R-IPSS,⁹ Global MD Anderson (MDA)¹⁰ model and low-risk MD Anderson Risk Model (LR-MDAS).¹¹ Those models successfully stratified MDS/MPN-U patients for OS and leukaemia-free survival (LFS), and R-IPSS was more

effective than others.¹² In this case, the patient was stratified as intermediate by R-IPSS.

MDS/MPN-U is an incurable disease with poor outcome, and treatment continues to be challenging. Ruxolitinib and azacytidine were used in a phase II trial in 35 MDS/MPN patients, demonstrating a response rate of 57%.¹³ After four cycles of ruxolitinib plus decitabine, the symptom response, spleen response, peripheral blood improvement, and decreased variant allele fraction of *KRAS* implied that this regimen was effective for MDS/MPN-U with *KRAS* mutation. *RAS* genes encode a family of 21-kDa proteins that belong to small guanosine triphosphate hydrolase enzymes and regulate cell proliferation and differentiation by activating the Raf/Mek/Erk and PI3K/Akt pathways, which are strongly associated with myeloid malignancies.^{14,15} In MDS/MPN, the RAS pathway promoted cell proliferation by causing granulocyte-macrophage colony stimulating factor hypersensitivity.¹⁶ In this case, the incremental VAF of the *KRAS* mutation might play an important role in disease progression. However, drugs targeting *KRAS* have not been applied in the clinic at present. As a Janus kinase (*JAK*)/2 inhibitor, ruxolitinib was also useful in haematological malignancies with RAS pathway hyperactivation because ruxolitinib could reduce STAT5 activation.^{17,18} STAT5 is important to maintain the overactivated RAS pathway, and ruxolitinib could reverse the expansion of immature myeloid cells and decrease autonomous colony-forming unit-granulocyte-macrophage formation to alleviate symptoms and reduce the spleen size by reducing STAT5 activation.^{17,18} Furthermore, previous research demonstrated that ruxolitinib markedly reduced the tumour cell proliferation of *KRAS*-mutated mice and decreased the *KRAS* activation gene signature.¹⁹ In addition, as a DNA hypomethylating drug, decitabine could upregulate microRNA-181c, which is downregulated by DNA methylation, to suppress K-RAS protein expression.²⁰ Reduced *KRAS* mutation expression induced by ruxolitinib plus decitabine likely contributed to the alleviation of the patient's symptoms, splenomegaly and peripheral blood cell counts.

Other drugs might be effective in the disease. Patients presenting with proliferative features, including leukocytosis and splenomegaly, can be treated with hydroxyurea to manage symptoms and control leukocytosis.²¹ However, the coexistence of proliferative features and cytopenia made HMAs more appropriate.²¹ Trametinib, an oral selective *MEK1* and *MEK2* inhibitor,²² acts downstream of *KRAS* to suppress signalling through the Raf/Mek/Erk

pathway.²³ This treatment potentially suppresses the Raf/Mek/Erk pathway to restrain cell proliferation.

Conclusion

In conclusion, our research indicated that the ruxolitinib plus decitabine regimen was effective in *JAK2*-negative but *KRAS*-positive patients by reducing STAT5 activation and upregulating microRNA-181c to decrease the VAF of *KRAS*. However, additional investigations of this regimen are warranted.

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Disclosure

The authors report no conflicts of interest in this work.

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