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Letters to the Editor

Co-Occurrence of Jak2-Positive Myelofibrosis and Bcr-Abl-Positive Chronic Myelogenous Leukaemia Treated with Combination of Tyrosine Kinase Inhibitors and Ruxolitinib

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To the editor.

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders caused by somatic mutations in the genes involved in the tyrosine kinase alterations, which activate signaling pathways leading to the expansion of myeloid cells. According to the different clinical and morphological features and the genetic aberrations reported in the WHO classification,[1] the MPNs are classified into Philadelphia (Ph) chromosome-positive chronic myeloid leukemia (CML) and Ph-negative MPNs (polycythemia vera, essential thrombocythemia, primary myelofibrosis (PMF). The affected genes include the BCR-ABL1 in CML and JAK2/CALR/MPL mutations in Ph-negative MPNs. Although these molecular aberrations are usually considered mutually exclusive, the co-expression of BCR-ABL1 translocation and JAK2/CALR mutation has been reported in several case reports (recently reviewed by Zanelli et al.),[2] and its contribution to the clinicopathologic phenotype is still unclear. Based on the time, the two genetic alterations may be identified simultaneously, or BCR-ABL1 translocation may be acquired after a long history of Ph-negative MPNs (median latency 9 years), or finally, Jak 2/Calr MPN may be subsequently detected in previously diagnosed CML (median latency 5.4 years).[3] Indeed, when Ph+ CML is present in conjunction with Ph-negative MPN, it plays a dominant role, so patients usually receive treatment with only tyrosine kinase inhibitor (TKI).[2] The second Ph-negative MPN is initially cryptic and becomes evident under the selective pressure of the TKI treatment, with progression to myelofibrosis reflecting an impact of clonal competition between the 2 MPNs and providing a rationale for combination treatment.[2-5] The availability of kinase inhibitors to target the two driver kinases, TKI for LMC and Ruxolitinib for patients with PMF, opens the question of whether the two-drug association represents an optimal therapeutic strategy in terms of feasibility, safety and tolerance. Starting from the presentation of a case that we have diagnosed and treated, we conducted a systematic review of the topic.

A 55–year–old man was referred to our center in 2019 because of splenomegaly, leucocytosis (white count cells 14.580/mm^3), mild thrombocytosis (Platelets 451000/mm^3), and increase of Lactate dehydrogenase. Cytogenetic analyses revealed the Caryotype 46, XY, t(9;22)(q34;q11.2)[4]/46, XY, and the molecular study documented concurrent BCR-ABL rearrangement (b3a2 and b2a2) and Jak-V617F mutation. The bone marrow (BM) was hypercellular with myeloid and megakaryocytic proliferation and a mild increase in reticulin fibrosis (grade 1). The clinicopathologic features of the patient are reported in **Table 1**. According to WHO, the double diagnosis of CML and Early Myelofibrosis was made. Consequently, Dasatinib therapy was started at 100 mg daily, associated with aspirin once daily. Deep molecular response (DMR) (MR 5.0) was achieved at 6 months and was associated with the normal size of the spleen and cell count. In March 2023, despite DMR during Dasatinib treatment, splenomegaly and persistent moderate anemia were documented. A new BM documented a significant increase in fibrosis (grade 3) with evolution to PMF in the advanced phase (**Figure 1**). The cytogenetic analysis showed del(20), and next-generation sequencing (NGS) detected several mutations (**Table 1**). The patient was classified as DIPSS grade 1, MIPSS70-plus version 2.0 high-risk MF and, consequently, a candidate for allogeneic stem cell transplant (SCT). In the meantime, in June 2023, Ruxolitinib was started at the dose of 15 mg twice. Dasatinib was maintained at a lowered dosage (50 mg/die) to manage the association and toxicity of the two drugs. During the 6 months of combination therapy, no hematological toxicity was noticed, and the DRM

Table 1. Summary of clinicopathologic features of the patient with the co-expression of BCR-ABL1 translocation and JAK2 mutation.

	CASE
AGE, YEARS	55
SEX	Male
FIRST PRESENTATION	Incidental findings of Leucocytosis, thrombocytosis and splenomegaly
WHITE BLOOD CELLS	14.580 x10^3/uL
HEMOGLOBIN	14.4 gr/dL
PLATLETS	496 000 x10^3/uL
LDH	590 mg/dL
SPLENOMEGALY	16 cm in length by ultrasound assessment
BONE MARROW	Hypercellular, myeloid hyperplasia, Megakaryocytic proliferation with atypia, reticulin fibrosis grades 1
KARYOTIPE	46,XY,t(9;22)(q34;q11.2)[4]/46, XY
qRT-PCR for BCR-ABL	BCR-ABL rearrangement (b3a2 and b2a2)
MOLECULAR TEST	JAK 2 V617F
DIAGNOSIS	CML and Early Myelofibrosis
TREATMENT	Dasatinib 100 mg daily associated with aspirin once daily
DISEASE COURSE	Deep molecular response (MR 5.0) was rapidly achieved at 6 months and maintained and associated with the normal size of the spleen and normal cell blood count
SECOND PRESENTATION	Anaemia, Leucocytosis, thrombocytosis, elevated LDH
TIME of SECOND PRESENTATION	41 months after the first diagnosis
WHITE BLOOD CELLS	15.190 x10^3/uL
HEMOGLOBIN	10.6 gr/dL
PLATLETS	449 000x10^3/uL
LDH	1127 mg/dL
SPLENOMEGALY	16 cm in length by ultrasound assessment
BONE MARROW	a significant increase in fibrosis (grade 3) with evolution to primary Myelofibrosis in the advanced phase
KARYOTIPE	46,XY, del(20)
MOLECULAR TEST	JAK 2 V617F
qRT-PCR for BCR-ABL	Deep molecular response (MR 5.0)
NGS	ETV6c.602T>C ETV6c.886G>A IDH1, ZRSR2
MIPSS70-PLUS VERSION 2.0 SCORE RISK for MF	High risk
TREATMENT and DISEASE COURSE	Ruxolitinib 15 mg x 2 daily associated with lowered dosage of Dasatinib (50 mg/die) for 6 months followed by allogenic SCT
FOLLOW-UP, months	66 months (12 after SCT)
OUTCOME	Alive with complete engraftment and no detectable BCR-ABL1 transcript or JAK2 mutation

CML: chronic myeloid leukemia; LDH: Lactate dehydrogenase; NGS: Next Generation Sequencing, SCT: stem cell transplant.

was maintained. In January 2024, the patient received SCT from an HLA-matched unrelated donor, obtaining a complete donor cell engraftment and complete remission.

Up to August 2024, a systematic PubMed search for publications in English allowed us to identify 87 cases with double aberrations and clinically relevant MPNs. So far, only 13 cases (present one included) of coexistence of Ph+CML and Ph-negative MPN disease were treated with an association of TKIs and Ruxolitinib (**Table 2**). Out of them, nine initially presented with Ph-negative MPN preceding CML (range 2.5-19 years following the first diagnosis, median 7 years). The CML preceded Ph-negative MPNs in 3 of the 13 cases (range 6 -29 months, median 12 months) during TKI treatment. Only in one case the CML and Ph-negative MPN were concomitant. At the time of the second presentation, the NGS detected several additional genetic aberrations in 4 of the 5 patients with NGS data available.

In most cases (11/13), the ruxolitinib was associated with ongoing TKI. In all eight patients with available data, the dosage of the TKI and Ruxolitinib was lowered

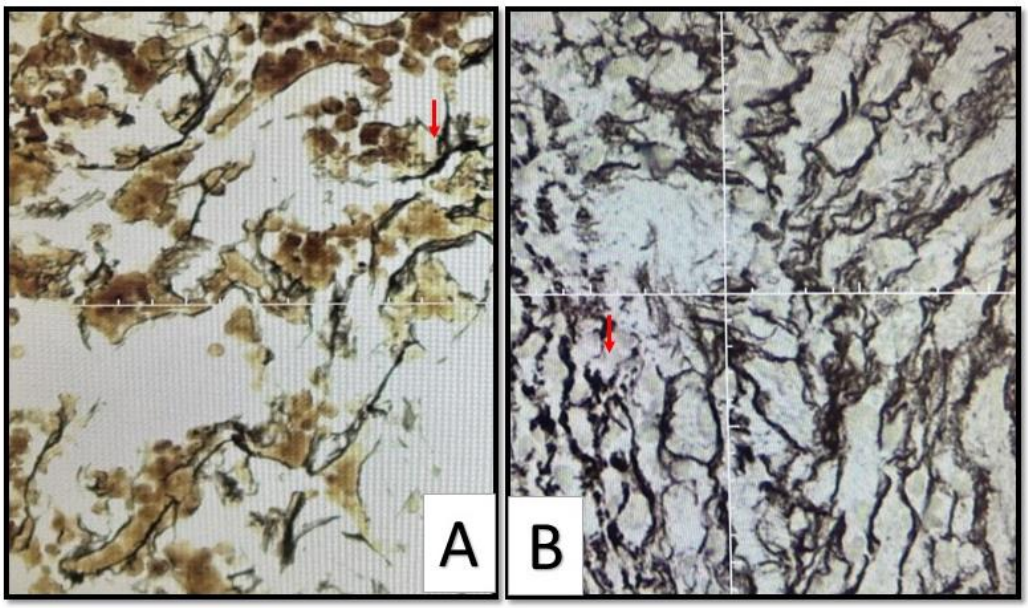

Figure 1
A: Bone marrow biopsy at diagnosis (2019) of simultaneous CML and early MF disease with grade 1 of fibrosis (staining with silver impregnation, 20x optical microscope)
B: Bone marrow biopsy after 4 years of tyrosine kinase inhibitor therapy (2023) showing predominant features of primary fibrosis in advanced phase with increase reticulin fibrosis of grade 3 (staining with silver impregnation, 20x optical microscope)

to manage the hematological toxicity. In particular, when both drugs were prescribed at full dosage, discontinuation was necessary (cases 2 and 12). On the other hand, when one of the two drugs was administered at a lowered dosage, an extra adjustment was required (cases 1,3,5,7,8). In our case, no more adjustment of dosage was necessary, probably because we initially prescribed a lower dose of both drugs. Out of the hematological toxicity, no other one was reported. Note that CML is rather easy to control; however, seven patients out of 13 on combination treatment underwent STC treatment in most cases because of the progression of myelofibrosis.

To date, kinase inhibitors are able to target the 2 driver kinases and to treat both MPNs are available, even if with different efficacy. Imatinib, the first TKI approved by the FDA in 2001, represents a milestone in CML therapy, and with the new-generation TKIs has revolutionized the treatment of CML patients, producing a molecular remission in most of case. Jak 1/JAK2 inhibitor Ruxolitinib is the first-in-class drug for molecular targeted therapy of intermediate and high-risk MF but with a modest effect on the evolution of the disease. Given the coexistence of two driver mutations in some patients and the availability of two target drugs, it is pivotal to understand the relative contribution of BCR-ABL1 and mutant JAK2/CALR in determining the clinicopathologic phenotype. In this regard, numerous prior reports have questioned the clonal composition of MPN harboring both Ph+ and Ph- driver mutations, with some studies favoring the presence of two independent clones and others supporting the hypothesis that the two genetic events occur in the same clones.[3,6] It is clear from prior studies that each of these proposed theories is possible, but the presence of two independent clones seems to represent the more common event.[2-5] The clinical presentation of two genetic aberrations may vary, being CML and Ph-negative MPN alternatively detecting them first or during the treatment. To date, the current scientific literature reports fewer than a hundred cases with clinically relevant coexistence of dual MPNs[2] and shows that Ph+ CML seems to play a clinically dominant role compared with the co-expressed Ph-negative clone. Consequently, patients often received a TKI only. CML is rather easy to manage, with an overall good response to different types of TKIs in most patients; however, an opposite growth of Ph+ CML and Ph-MPN clones was often observed under TKI treatment. The control of Ph+ clone by TKI therapy could unmask the second Ph-negative MPN phenotype with a propensity to accelerate the fibrosis (the median latency is 5.4 years when CML preceding Ph-negative MPN vs 9 years when Ph-negative MPN preceding CML) and supports the theory that the two clones are not only independent and unrelated but could also compete with each other and provide a rationale for combination treatment.[7-9] Because of the rarity of the condition, standardized treatment for dual MPN has not been established. Our systematic review allowed to highlight 13 cases with co-occurrence of two driver mutations associated with clinically relevant MPNs and treated with a combination of both classes of drugs, TKI and Ruxolitinib. The use of "combination therapy" was demonstrated to be feasible and safe but required an

Table 2. Combination therapy of tyrosine kinase inhibitors and the Jak 2 inhibitor (Ruxolitinib) in patients with concurrent Jak2/Calr-positive Myeloproliferative disorder and Chronic Myelogenous Leukaemia (CML).

REFERENCES			PATIENT	DIAGNOSIS *	TIME TO SECOND DIAGNOSIS	DRIVER MUTATIONS	KARYOTYPE or OTHER MUTATIONS	TKI	RUXO DOSAGE	DOSE ADJUSTMENT	TIME of TKI and RUXO ASSOTIATION	OUTCO
Iurlo A et al 2014 (4)			Case 1 Case 2	PV evolved in post-PV MF and CML PV evolved in post-PV MF and CML	19 years 12 years	Bcl-Abl1 and Jak 2-V6177F Bcl-Abl1 and Jak 2-V6177F	Normal karyotype; NGS N.D. Normal karyotype; NGS N.D.	Imatinib (400 mg/day) Imatinib (400 mg/day)	15 mg BID 20 mg BID increased at 25 mg	Reduction of Ruxo dosage at 10 mg and Imatinib at 300 mg for hematological toxicity (grade 3 anemia and grade 1 thrombocytopenia) discontinuation for hematological toxicity (grade 3 anemia and grade 3 thrombocytopenia)	10 months 2 months	clinical alive in remissio
Zhou A et al 2015 (5)			Case 3	PV evolved in post-PV MF and CML	10 years	Bcl-Abl1 and Jak 2-V6177F	N.D.	Dasatinib (100 mg/die)	10 mg BID	Reduction of Ruxo dosage to 10 mg alternating with 5 mg	3 years	stable a combina
Kandarpa e al 2017 (7)			Case 4 Case 5	post-PV MF and CML CML and MF	2.5 years 2.5 years	Bcl-Abl1 and Jak 2-V6177F Bcl-Abl1 and Jak 2-V6177F	None NRAS, SRSF2, IDH2,EZH2, ASXL1	Imatinib and Dasatinib Nilotinib	N.A. N.A	N.A. Alternating schedule of Nilotinib (4 days on/1 day off, then Ruxolitinib (1 days on/1 day off)	more than 1 year more than 1 year	clinical clinical
Boddu P et al 2018 (8)			Case 6	MF and CML	2.5 years	Bcl-Abl1 and CALR	del (20q); NGS N.D.	Imatinib	N.A.	N.A.	2 months	alive in remissio
Sora F et al 2021 (11)			Case 7	CML and MF	6 months	Bcl-Abl1 and CALR	ASXL1 and ZRSR1	Nilotinib (600mg)	10 mg BID	Dose Reduction of Ruxo and Nilotinib for hematological toxicity	4 years	died aft progress (hepato requiren
Ryu J et al 2022 (12)			Case 8	MF and CML in accelerated-phase	7 years	Bcl-Abl1 and Jak 2-V6177F	t(12-19); NGS N.D.	Imatinib	N.A.	N.A.	1.5 months	Poor res
Zhao Y et al 2022 (9)			Case 9 Case 10 Case 11	MF and CML MF and CML CML and MF	4 years 5 years 1 years	Bcl-Abl1 and Jak 2-V6177F Bcl-Abl1 and Jak 2-V6177F Bcl-Abl1 and Jak 2-V6177F	der (14-21); NGS N.D. 47 XY,+8; NGS N.D. N.D.	Imatinib, switched to Nilotinib, Sunitinib, Ponatinib, Dasatinib, Nilotinb Nilotinib	N.A. N.A. N.A.	N.A. N.A. N.A.	N.A. 17 26 months	alive in remissio alive in remissio Poor cli and TK
Zhang Y. et al 2022 (10)			Case 12	ET evolved in post-ET MF and CML in	11 years	Bcl-Abl1 and Jak 2-V6177F	del (13); IDH1, IDH2,ASXL1, KRAS, RUNX1	Imatinib and Fumatinib	20 mg BID	Imatinib discontinued for toxicity	N.A.	Poor res eligible

				accelerated-phase								
Our case			Case 13	CML and early MF evolved in MF	concomitant	Bcl-Abl1 and Jak 2-V6177F	del(20)(q12); ETV6c.602T>C ETV6c.886G>A IDH1, ZRSR2	Dasatinib (50 mg/die)	15 mg BID	No more adjustment	13 months	alive in remissio

* The 1st disease listed is the first one diagnosed. BID: two times a day; CML: Chronic myeloid leukaemia; ET: Essential Thrombocythemia; N.A: no available; N.D. not done; NGS Next Generation Sequencing; PV: Polycythemia Vera; MF: Myelofibrosis; Ruxo: Ruxolitinib; SCT: stem cell transplant; TKI: tyrosine kinase inhibitor.

adjustment in the dosage of both drugs to control the hematological toxicity and avoid discontinuation. Moreover, although the TKI are very effective for CML, the jak1/jak2 inhibitors are not similarly active to target Ph- negative clone. Thus, although one component of the patient's disease may be adequately treated, the second genetic alteration may not be. In addition, at the time of the second MPN diagnosis, the cytogenetic analysis and NGS may often detect additional somatic mutations, which are associated with high genetic instability and predict poor survival due to MPN-Ph negative disease. Indeed, most of the patients treated by the two-drug association also received SCT due to anticipated poor survival associated with the progression of myelofibrosis MPN-Ph negative disease.[2,11]

In conclusion, the data suggests that patients with concurrent Ph+ CML and Ph-MPN disease may have genetic instability and a tendency to develop progression of fibrosis with an unpredictable and poor outcome. The use of combination therapy with TKI and Ruxolitinib for the treatment of these patients is feasible and safe after a dosage adjustment of both drugs to avoid pharmacology toxicity. However, Ruxolitinb is effective to reduce the spleen volume but not to prevent the fibrosis progression threrefore in association with TKI it could represent a possible bridge to allogeneic transplant.

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