Blast phase myeloproliferative neoplasm with prior exposure to ruxolitinib: comparative analysis of mutations and survival

The International Consensus Classification (ICC) recognizes a *JAK2* mutation-prevalent category of myeloproliferative neoplasms (MPN), which includes polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), and MPN, unclassifiable (MPN-U).[1,2] Each one of these MPN subcategories is at risk of progressing into acute myeloid leukemia (AML) with reported rates (median follow-up) of 3.9% (8.2 years) for PV, 2.6% (9.9 years) for ET and 9.3% (3.2 years) for PMF.[3] There is limited information regarding the risk of leukemic transformation in MPN-U.[4] MPN progression into AML is operationally designated as blast-phase disease (MPN-BP) and requires the presence of ≥20% circulating or bone marrow (BM) blasts while a blast count of 10-19% constitutes "accelerated phase" disease.[2]

In a previous study of 410 patients with MPN-BP, including 248 from the Mayo Clinic, we reported a median survival of 3.6 months and 3-year survival rate of 6%.[5] Among the Mayo Clinic cases, 121 (49%) received supportive care, 103 (42%) chemotherapy with (n=24) or without (n=79) achieving response, and 24 (10%) allogeneic stem cell transplant (ASCT);[5] the 1/3-year survival rates were 66%/32% for ASCT, 37%/19% for patients achieving chemotherapy-induced response but were not transplanted, and 8%/1% in the absence of both ASCT and response to chemotherapy.[5] The particular study preceded the advent of Janus kinase 2 inhibitors (JAKi), which are now part of the expanding therapeutic armamentarium for MPN.[6] In this regard, ruxolitinib has paved the way with its Food and Drug Administration (FDA) approval in 2011.[7] There is currently general agreement on the efficacy of ruxolitinib and other JAKi in controlling splenomegaly and constitutional symptoms of patients with MPN whereas there is limited evidence for value in modifying disease natural history, including impact on progression into MPN-BP.[6] The current retrospective study details our more recent experience in patients with MPN-BP who were diagnosed after the approval date for ruxolitinib (2011); our main objective was to examine the impact of prior exposure to ruxolitinib, on genetic composition and survival.

The current study was conducted under an Institutional Review Board-approved minimum risk protocol that

Table 1. Cytogenetic and mutation information on 103 patients with myeloproliferative neoplasms with transformation into acute myeloid leukemia (blast phase disease): variables collected at the time of leukemic transformation, stratified by prior exposure to ruxolitinib or other Janus kinase 2 inhibitors.

Variables	All patients N=103	Exposed to ruxolitinib N=32	Not exposed to ruxolitinib/other JAKi N=71	*P*
Karyotype, N evaluable =97				0.34
Normal, N (%)	17 (17.5)	4 (14.2)	13 (18.8)	0.58
Complex karyotype, non-monosomal, N (%)	18 (18.5)	7 (25)	11 (15.9)	0.3
Monosomal karyotype or monosomy 7, N (%)	35 (36)	7 (27)	28 (40.5)	0.14
Other, N (%)	27 (27.8)	10 (35)	17 (24.6)	0.27
Driver mutation				0.65
JAK2, N (%)	69 (67)	24 (75)	45 (63)	
MPL, N (%)	6 (5.8)	2 (6)	4 (5)	
CALR, N (%)	7 (6.7)	2 (6)	5 (7)	
Triple-negative, N (%)	1 (0.9)	0 (0)	1 (1.4)	
JAK2 wild-type but *CALR/MPL* not evaluated, N (%)	20 (19.4)	4 (12.5)	16 (22.5)	
Somatic mutations, N evaluable =96, N (%) (seen in 7 or more patients)	43 (41)	11 (34)	32 (45)	0.3
ASXL1	17 (39.5)	3 (9)	14 (19.7)	0.17
TP53	14 (32.5)	3 (9)	11 (15.4)	0.38
TET2	8 (18)	1 (3)	7 (9.8)	0.2
FLT3	8 (18)	1 (3)	7 (9.8)	0.2
SRSF2	7 (16)	5 (15.6)	2 (2.8)	0.02
EZH2	7 (16)	2 (6)	5 (7)	0.88

JAKi: Janus kinase 2 inhibitor.

allowed retrospective collection and analysis of data from patients seen at the Mayo Clinic Rochester, MN, USA, after the FDA approval date for ruxolitinib (2011); diagnosis dates spanned from 12/16/2011 to 5/27/2021. Diagnoses of specific MPN variants and MPN-BP were according to ICC criteria.[2] For the purposes of comparative analysis, patients were classified into those with or without prior exposure to ruxolitinib (Tables 1 and 2). Responses were recorded according to European LeukemiaNet criteria.[8] Clinical and laboratory data, including cytogenetic and molecular information, were collected from patients at the time of leukemic transformation. Survival analysis was calculated from the time of leukemic transformation to death or last follow-up. Conventional statistical methods were applied using JMP Pro 16.0.0 software (SAS Institute, Cary, NC, USA).

A total of 103 patients (median age 70 years, range 37-89; 52% males) were considered; MPN variant prior to AML transformation was PMF in 35% and post-PV/ET MF in 65% (Table 1). MPN treatment prior to leukemic transformation included ruxolitinib ± other JAKi in 32 (31%) patients while the remaining 71 cases received other cytoreductive drugs, mostly in the form of hydroxyurea and not including JAKi (n=60; 58%) or neither (n=11; 10%). Median duration of treatment for the ruxolitinib and non-ruxolitinib groups were 47 and 66 months, respectively (P=0.06), and median time from MPN diagnosis to leukemic transformation was 6 and 8 years (P=0.47). At the time of leukemic transformation, karyotype was available in 97 patients and revealed monosomal karyotype or monosomy 7 in 35 (36%), complex karyotype, non-monosomal in 18 (19%), normal karyotype in 17 (18%) and other abnormalities in 27 (28%); karyotype profile was similar between the ruxolitinib and non-ruxolitinib groups (P=0.34). Driver mutation distribution ("N" evaluable =83) was also similar in the two groups (P=0.65): *JAK2* 67%, *CALR* 7%, *MPL* 6% and triple-negative 1%. The frequency of other mutations is outlined in Table 1 with the most frequent being *ASXL1* (40%), *TP53* (33%), *TET2* (18%), *FLT3* (18%), *SRSF2* (16%), *EZH2* (16%), *DNMT3A* (16%), *IDH1* (16%), *RUNX1* (11%) and *NRAS* (9%); frequency of *SRSF2* mutation was significantly higher in the ruxolitinib group (P=0.02; 16% *vs*. 3%; Table 1); other mutations of similar distribution, not listed in Table 1 and occurring in less than seven patients each, included *DNMT3A, IDH1, IDH2, RUNX1, NRAS, STAG2, ZRSR2, GATA2, U2AF1, CEBPA, NPM1, KIT, WT1, SF3B1, BCOR, FGFR3*. Red cell transfusion need (P<0.01), antecedent PMF history (P<0.01) and marked splenomegaly (P<0.01) were also more likely to be seen in the ruxolitinib group (Table 1).

First-line MPN-BP therapy included intensive chemotherapy (n=35; 35%), hypomethylating agents (HMA) with (n=12; 12%) or without (n=21; 21%) venetoclax, other drugs (n=6; 6%) or supportive care (n=25; 25%) (Table 2; P=0.72 for ruxolitinib *vs*. non-ruxolitinib groups). Seventy-one patients were evaluable for response to chemotherapy with only 11 (15%) achieving complete remission/complete remission with incomplete count recovery (CR/CRi) (Table 2). At the time of this writing, 96 (93%) deaths and 11 (11%) ASCT were documented, without significant differences between ruxolitinib *versus* non-ruxolitinib groups (Table 2). Among the seven patients censored alive, five had received ASCT, four of whom had persistent bone marrow blasts (8-16%) at time of transplant. Univariate survival analysis disclosed favorable impact from ASCT (P<0.01) and achievement of CR/CRi (P<0.01) while inferior survival was associated with age >65 years (P=0.02), complex/monosomal karyotype (P<0.01), platelet count <100x10^9/L (P=0.01), and previous

Table 2. Treatment approaches and clinical course of 103 patients with myeloproliferative neoplasms with transformation into acute myeloid leukemia (blast phase disease), stratified by exposure to ruxolitinib or other Janus kinase 2 inhibitors.

Variables	All patients N=103	Patients exposed to ruxolitinib N=32	Patients not exposed to ruxolitinib/other JAKi N=71	*P*
Time from MPN diagnosis to AML in years, median (range)	7.5 (0-36)	6 (1-33)	8 (0-36)	0.47
First-line AML therapy, N evaluable =99				0.72
Supportive care, N (%)	25 (25.2)	9 (29)	16 (23)	
Hypomethylating agents alone, N (%)	21 (21.2)	7 (22)	14 (20)	
Venetoclax plus hypomethylating agents, N (%)	12 (12.1)	5 (16)	7 (10)	
Induction chemotherapy, N (%)	35 (35.3)	9 (29)	26 (38)	
Imetelstat, N (%)	6 (6)	1 (3)	5 (7)	
AML therapy response, N evaluable =71				
CR/CRi, N (%)	11 (15)	5 (17.8)	8 (12.6)	0.52
ASCT, N evaluable =103, N (%)	11 (10.6)	3 (9)	8 (11.2)	0.77
Deaths, N (%)	96 (93)	31 (96.8)	65 (91.5)	0.28

MPN: myeloproliferative neoplasms; AML: acute myeloid leukemia; JAKi: Janus kinase 2 inhibitor; CR/Cri: complete remission/complete remission with incomplete count recovery; ASCT: allogeneic stem cell transplant.

exposure to ruxolitinib (*P*=0.047). Multivariable analysis confirmed the favorable impact of ASCT (*P*<0.01; hazard ratio [HR]=0.18; 95% confidence interval [CI]: 0.08-0.41) and the adverse impact of complex/monosomal karyotype (*P*<0.01; HR=2.2; 95% CI: 1.4-3.5), platelet count <100x10^9/L (*P*<0.01; HR=2.3; 95% CI: 1.4-3.6) and previous exposure to ruxolitinib (*P*=0.04; HR=1.7; 95% CI: 1.02-2.7; Figure 1A); the latter was most apparent in the absence of ASCT (Figure 1B). Figure 1C depicts survival data stratified by ASCT *versus* intensive chemotherapy without ASCT *versus* less intensive chemotherapy including HMA alone or in combination with venetoclax. Among the 32 ruxolitinib-exposed patients with MPN-BP, 31 had died and causes of death included progressive leukemia in 26 patients, pneumonia/infections in three and subarachnoid hemorrhage and granulocytic sarcoma in one patient each.

In the current contemporary series of patients with MPN-BP, there was no evidence to suggest improved outcome in the last decade while the value of ASCT in securing long-term survival and the detrimental impact of high-risk karyotype and thrombocytopenia were confirmed.[5] The favorable impact of ASCT in MPN-BP was recently asserted by a large European Bone Marrow Transplant (EBMT) registry data involving 663 informative cases, with 3-year survival rate of 36%.[9] In the particular study, the absence of active disease at time of transplant was associated with a higher 3-year survival rate (43% *vs*. 30%) and, therefore, supportive of current practice of using hypomethylating agent-based combination therapy, as a bridge towards ASCT.[10,11] The novel observation in the current study was the identification of prior exposure to ruxolitinib as an independent risk factor for inferior survival, independent of its observed association with *SRSF2* mutation. However, this does not prove cause and effect and our observations should be interpreted with caution, considering the retrospective nature of the study. In this regard, we acknowledge missing information on details of ruxolitinib therapy, including indications and pretreatment risk score, although such information might be more relevant for post-ruxolitinib treatment survival as opposed to post-MPN-BP survival. Possible explanations outside of drug effect include the enrichment of biologically more aggressive disease in patients needing treatment with ruxolitinib, which might not have been accounted for by risk factors considered in our multivariate model, which, however, did account for the preponderance of pre-PMF and transfusion-dependent cases in the ruxolitinib-exposed patients. The potential value of ASCT in mitigating adversity from known

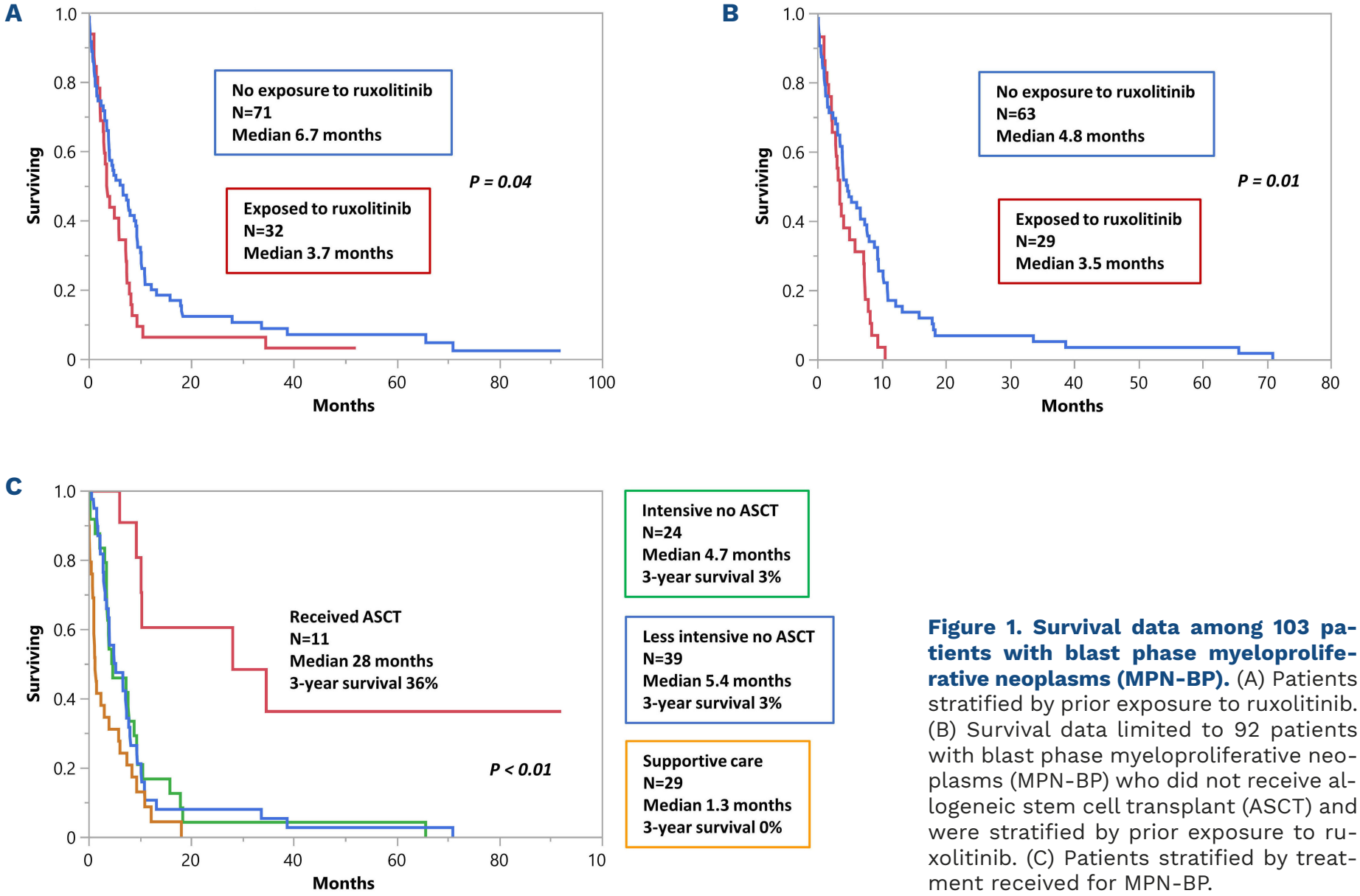

Figure 1. Survival data among 103 patients with blast phase myeloproliferative neoplasms (MPN-BP). (A) Patients stratified by prior exposure to ruxolitinib. (B) Survival data limited to 92 patients with blast phase myeloproliferative neoplasms (MPN-BP) who did not receive allogeneic stem cell transplant (ASCT) and were stratified by prior exposure to ruxolitinib. (C) Patients stratified by treatment received for MPN-BP.

or unknown risk factors for survival in MPN-BP requires validation from a larger study.

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Contributions

All authors reviewed and approved the manuscript. MGA, AT and NG designed the study, abstracted clinical and laboratory data, performed statistical analysis, and wrote the paper. AT, AAK, KHB, WJH, MRL, AAM, MSP, MAE, HA, AP and NG contributed patients. MS, MTH, and KKR participated in pathology review. RPK participated in cytogenetic review.

Data-sharing statement

Data will be shared upon reasonable request to the corresponding author.

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