To the editor:

In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology

Controlled studies in polycythemia vera (PV) have demonstrated the value of aggressive phlebotomy, aspirin, and cytoreductive therapy in preventing thrombotic complications.[1-3] In the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) prospective study of 1638 patients diagnosed by using criteria from the Polycythemia Vera Study Group, risk factors for all thromboses were age older than 65 years and prior thrombotic events.[4] However, diagnosis criteria for PV have since undergone substantial revision in the World Health Organization system for disease classification, with special emphasis on bone marrow morphology and *JAK2* mutational status.[5] Accordingly, this study includes 1545 patients with strictly World Health Organization–defined PV who were diagnosed and followed up in 7 centers in Italy, Austria, and the United States that belong to the International Working Group for Myeloproliferative Neoplasms. The study was approved by the institutional review board at each institution. Objectives were to (1) describe the rate of thrombosis, (2) report the sites and frequency of recurrences after a first arterial or venous event, and (3) identify risk factors for arterial vs venous thrombosis.

The characteristics of the cohort recruited at diagnosis (Table 1) reflect the heterogeneity of epidemiologic and clinical features that are found in the routine clinical practice of diagnosing PV. Arterial and venous thrombosis history before or at diagnosis was documented in 246 (16%) and 114 (7.4%) patients, respectively. The frequencies of arterial and venous thrombosis were lower than those recorded in the ECLAP study[4] (27% and 11%, respectively) but comparable to those reported in the recent Cyto-PV study[2] (arterial 17%, venous 12%). Major hemorrhage before or at diagnosis was reported in 4.5% of patients in this study vs 8% in ECLAP and 1.7% in Cyto-PV cohorts. The prevalence of hypertension, hyperlipidemia, diabetes, and tobacco use was similar to that reported in the ECLAP and Cyto-PV studies.

Median follow-up was 6.9 years, and treatment included aspirin (84%) and cytoreductive agents (73%), in addition to phlebotomy (Table 1). Postdiagnosis total major thrombosis rate was 2.62% patients per year, lower than that reported in the ECLAP trial (4.4% patients per year) but comparable to the rate in the Cyto-PV study (2.7% patients per year) in which management of cardiovascular risk factors was more intensive than in the ECLAP study.

Arterial or venous thrombosis occurred in 184 (12%; rate: 1.59% patients per year) and 137 (9%; rate: 1.05% patients per year) patients, respectively. In addition, in 75% of the patients, arterial events were associated with subsequent arterial events, and in the remaining 25%, they were associated with venous thrombosis including splanchnic vein events. Conversely, in patients with prior venous events, 61% had venous recurrences and 39% had arterial recurrences. In multivariable analysis, previous arterial event (hazard ratio [HR], 1.7; 95% confidence interval [CI], 1.2 to 2.4) and hypertension (HR, 1.6; 95% CI, 1.2 to 2.2) were significantly associated with subsequent arterial events whereas previous venous event (HR, 2.6; 95% CI, 1.5 to 4.4) and age ≥65 years (HR, 1.7; 95% CI, 1.2 to 2.5) were significant predictors of future venous thrombosis.

A potential limitation of our study is its retrospective design; however, the strength is the large sample size, the well-defined patient population, the evaluation at diagnosis, and the long follow-up period. The frequencies of events in our study were similar to those reported in the Cyto-PV[2] study and generally lower than those reported in the ECLAP[4] study. It is possible that this reflects a change of clinical epidemiology in contemporary PV patients, but note that these different studies are not necessarily comparable, although earlier diagnosis and treatment, improved management of cardiovascular risk factors, and more appropriate use of cytoreductive drugs, aspirin, and phlebotomy might have contributed to the improved outcome in this study. Regardless, such details are important to consider for future clinical trials in PV. Of note, patients with a prior venous thrombosis had a more frequent subsequent recurrence in the venous district but a proportion of them (39%) also experienced arterial events and vice versa. This finding may have practical implications and suggests antiplatelet therapy and anticoagulant therapy (vitamin K antagonists or direct factor X inhibitors) as the favorite choice to prevent arterial and venous thrombosis, respectively, but also suggests studies of antithrombotic drug combinations. In this regard, statins that are specifically targeted to prevent arterial thrombosis and also seem promising for reducing risk of venous thrombosis[6] may be candidates to be tested in addition to recommended therapy. The concept of combination therapy is further supported by the fact that currently reported rates of recurrent thrombosis in PV have not improved that much over those reported in much earlier Polycythemia Vera Study Group studies.[7]

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Table 1. Patients' characteristics at diagnosis and during follow-up

Characteristic	No. evaluable	No. of patients	%	95% CI
At diagnosis				
Age, years	1545			
Median		61		
Range		18-95		
Sex	1545			
Male		760	49	
Female		785	51	
Hemoglobin, g/dL	1545			
Median		18.4		
Range		15.1-26.5		
Hematocrit, %	1545			
Median		55		
Range		36-78		
Leukocyte count, $\times 10^9$/L	1545			
Median		10.4		
Range		3-171.6		
Platelet count, $\times 10^9$/L	1545			
Median		466		
Range		7-2370		
JAK2*V617F* mutation	1268	1239	98	
Pruritus	1349	485	36	
Vasomotor symptoms	1412	403	29	
Palpable spleen	1477	534	36	
History of tobacco use	1301	206	16	
History of diabetes	1149	97	8	
History of hyperlipidemia	1073	196	18	
History of hypertension	1388	638	46	
Leukoerythroblastic smear	1056	63	6	
Abnormal karyotype	631	77	12	
Arterial thrombosis before/at diagnosis	1545	246	16	
Acute myocardial infarction	1545	65	4	
Stroke/transient ischemic attack	1545	138	9	
Peripheral arterial thrombosis	1545	29	2	
Other/unknown	1545	14	1	
Venous thrombosis before/at diagnosis	1545	114	7	
Deep vein thrombosis/pulmonary embolism	1545	78	5	
Splanchnic thrombosis	1545	30	2	
Other/unknown	1545	6	0	
Major hemorrhage before/at diagnosis	572	24	4	
Follow-up				
Years of follow-up	1545			
Median		6.9		
Range		0-39		
Treatments				
Cytoreductive therapy*	1545	1129	73	
Aspirin therapy	1535	1281	84	
Total thrombosis	1545	290	19	
Incidence rate, % patients per year			2.62	2.34-2.94
Arterial thrombosis	1545	184	12	
Incidence rate, % patients per year			1.59	1.38-1.84
Acute myocardial infarction	1545	35	2	
Stroke/transient ischemic attack	1545	104	7	
Peripheral arterial thrombosis	1545	34	2	
Other/unknown	1545	11	1	
Venous thrombosis	1545	137	9	
Incidence rate, % patients per year			1.05	0.88-1.25
Deep vein thrombosis/pulmonary embolism	1545	88	6	
Splanchnic thrombosis	1545	27	2	
Other/unknown	1545	22	1	
Fatal cardiovascular events	1545	51	15	
Myelofibrosis/acute myeloid leukemia transformations	1545	174	11	
Incidence rate, % patients per year			1.42	1.22-1.65
Death	1545	347	23	
Incidence rate, % patients per year			2.74	2.46-3.04

CI, confidence interval.

*Cytoreductive treatments included hydroxyurea, interferon, busulfan, pipobroman, ^{32}P, anagrelide.

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To the editor:

Cryptic *XPO1-MLLT10* translocation is associated with *HOXA* locus deregulation in T-ALL

Biological subclasses of T-cell acute lymphoblastic leukemia (T-ALL) can be defined by recurrent gene expression patterns, which typically segregate with specific chromosomal anomalies. The HOXA$^+$ subgroup is characterized by deregulated homeobox A (*HOXA*) gene expression and is associated with translocations involving the mixed lineage leukemia (*MLL*) and/or *MLLT10* loci, *SET-NUP214*, or *TCRB-HOXA*.[1,2] Nevertheless, the genetic basis for many HOXA$^+$ cases remains unexplained.

Diagnostic assessment of a 33-year-old man with T-ALL revealed high leukemic blast expression of *HOXA9* at levels comparable to those in known HOXA$^+$ cases (Figure 1A). Tests for *PICALM-MLLT10*, *SET-NUP214*, *MLL-AF6*, and *TCRB-HOXA* were negative. Leukemic cells exhibited a complex karyotype (46,XY,add(2)(p14),-10,-17,+2mars,inc[11]), which led us to speculate that HOXA positivity might be caused by a structural genetic abnormality. We therefore performed poly(A)-enriched sequencing (RNA-sequencing) of diagnostic RNA, analysis of which revealed fusion of exon 24 of *XPO1* to exon 6 of *MLLT10* (Figure 1B, upper panel). Expression of an in-frame *XPO1-MLLT10* fusion transcript was confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) and direct sequencing (Figure 1B, lower panel).

We hypothesized that the common involvement of *MLLT10* would result in similar deregulation of *HOXA* locus expression in *XPO1-MLLT10*$^+$ and *PICALM-MLLT10*$^+$ T-ALL. We tested the expression of a range of *HOX* genes by quantitative RT-PCR. As predicted, the pattern of *HOXA* gene transcription in the *XPO1-MLLT10*$^+$ case was very similar to that in the *PICALM-MLLT10*$^+$ cases (Figure 1C). A targeted RT-PCR screen of 84 HOXA$^+$ T-ALL samples that lacked known explicatory genetic anomalies identified no further *XPO1-MLLT10*$^+$ cases (Figure 1D), suggesting rarity and/or breakpoint heterogeneity.

Each of the genes involved in this fusion has been previously implicated in leukemia. Notably, *MLLT10* (which encodes the AF10 protein) is involved in the recurrent *PICALM-MLLT10*[3] and *MLL-MLLT10*[4] translocations in both T-ALL and acute myeloblastic leukemia. Recently reported results of RNA-sequencing have identified *HNRNPH1* and *DDX3X* as *MLLT10* fusion partners in HOXA$^+$ T-ALL.[5] Our data provide further evidence of shared fusion partner–independent mechanisms of AF10-mediated transcriptional dysregulation, and this case adds to the repertoire of MLL and/or AF10-rearranged T-ALL that might be candidates for targeted DOT1L-directed therapy.[6] *MLLT10* breakpoints are heterogeneous, and increasing truncation of the transcript was reported to correlate with an earlier maturation block in T-ALL, although this was not confirmed in a later series.[3,7] In this case, detailed characterization of T-cell receptor (*TR*) gene configuration revealed monoallelic *TRG* and *TRD* and incomplete *TRB* diversity-joining rearrangements (data not shown), consistent with an immature pre-β-selection immunogenotype.[8]

XPO1 (also *CRM1*) encodes exportin 1, a transport protein that mediates nuclear export of multiple tumor suppressor and growth regulatory molecules (eg, P53 and RB1). Pharmacologic XPO1 inhibition has shown promising antileukemic activity in preclinical models via a mechanism that is believed to involve either nuclear retention of XPO1 cargo upon which the leukemic cells depend for survival,[9] and/or reactivation of nuclear protein phosphatase 2A.[10] It is tempting to speculate that HOXA-independent activity of the XPO1-AF10 fusion protein could also contribute to leukemogenesis in this case, for example through aberrant transport of proteins that mediate proliferation and survival and/or by dominant negative inhibition of wild-type XPO1.

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