Advanced Techniques in Biology & Medicine

Ianotto, Adv Tech Biol Med 2017, 5:2
DOI: 10.4172/2379-1764.1000224

Review Article OMICS International

Screening for MPN Mutations in Cases of Deep Vein Thrombosis and/or Pulmonary Embolism: What We have learnt from Studies

Jean-Christophe Ianotto[1,2]*

[1]Service d'Hématologie Clinique, Institut de Cancéro-Hématologie, CHRU de Brest, France
[2]EA3878 GETBO (Groupe d'étude de la thrombose en Bretagne occidentale), CHRU de Brest, France

Abstract

Myeloproliferative neoplasms (MPN) are chronic myeloid disorders characterized by a high-risk of thrombosis. One-third is in venous vessels. Clinicians who treat patients experiencing thromboses in such vessels know the high rate of cancer in such situation. Many studies have been published concerning the screening for mutations that drive MPNs (mostly JAK2V617F and CALR mutations) in case of deep vein thromboses and/or pulmonary embolism.

We reviewed the results of the studies published since 2005 (year of discovery of JAK2V617F, the most frequent of these mutations) and we analyzed the prevalence of mutations among the patients and their characteristics.

Sixteen studies have been published on this topic. Of 2907 patients, 39 (1.3%) were positive for JAK2V617F, reaching 2.1% in case of history of recurrence. CALR mutations have not been found in any of the studied situations. Women represent 73.5% of the cases. Patients over the age of 60 account for 76.5% of the cases. Only 10 (29.4%) of the patients have been identified to have MPN despite a median follow-up period of 42 months. All had thrombocytosis or polycythemia at the time of the thrombosis. Nineteen patients experienced thrombotic recurrence, describing JAK2V617F mutation as a pro-thrombotic factor.

Screening for JAK2V617F or CALR mutations should not be systematically performed for patients experiencing deep vein thromboses and/or pulmonary embolism because of the low rate of positivity. Attention should perhaps be focused on patients with persistent thrombocytosis or polycythemia who have a higher rate of MPNs. For the other positive cases with no features of MPN, the management is unclear, but a thorough evaluation by a hematologist should be performed, and the patients should be followed for years.

Keywords: JAK2V617F mutation; CALR mutations; Deep vein thrombosis; Pulmonary embolism; Myeloproliferative neoplasms

Abbreviations: CALR: Calreticulin; DVT: Deep Vein Thromboses; EPO: Erythropoietin; ET: Essential Thrombocythemia; MPN: Myeloproliferative Neoplasm; PE: Pulmonary Embolism; PMF: Primary Myelofibrosis; PV: Polycythemia Vera

Introduction

Philadelphia-negative myeloproliferative neoplasms (MPNs) are clonal hematopoietic disorders, including polycythemia Vera (PV), Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF). Three driver mutations have been identified as inducers of these diseases: JAK2V617F (95-97% of PV and 50-60% of ET and PMF patients), Calreticulin (CALR) and MPL mutations (20-30% and 2-5% of ET or PMF patients, respectively). JAK2 is a tyrosine-kinase bind to the intra-cellular part of the EPO-receptor. JAK2V617F is a somatic acquired mutation, located in its pseudo-kinase domain which transforms JAK2 in a gain-of-function enzyme, by continuous activation of the kinase domain despite the low level of circulating EPO. It induces an independent growth from cytokines (i.e., EPO for immature red cells) and a hypersensibility to these cytokines (if they are added to cells cultures) [1]. The result is an increase of mature cells in bone marrow and blood, inducing hyperviscosity and thromboses which are the main complications (20 to 50% of the patients). Ten to fifteen percent of MPNs are diagnosed at the time of a thrombotic event. Venous thromboses represent one-third of these events [2].

The clinicians (mostly non-hematologists) who treat people experiencing thromboses are constantly searching for the etiology, to adapt the treatment to each case and to prevent recurrence. If arterial thrombotic events are mostly due to arteriosclerosis (cardio-vascular risk factors should be identified, i.e., hypertension, diabetes mellitus, hypercholesterolemia…), venous thrombotic events are more relating to extrinsic compression (i.e., solid or hematological cancers) or perturbation of the bloodstream (i.e., hyperviscosity by an increase of circulating cells or pro-coagulant status like inflammation...).

In the general population, deep vein thrombosis with or without pulmonary embolism (DVT/PE) are the most frequent venous thrombotic sites. The diagnoses can be made with a good clinical exam evaluating the Wells score (or assimilated) plus quantification of D-dimers and realization of duplex ultrasound for lower legs DVT and/or CT angiography for PE [3]. These sites have been widely studied for the presence of hidden or obvious cancers, such as MPNs. The research of those mutations is quite easy because it just requires blood sample but could be time consuming with a usual timing of two to four weeks to receive the results.

Because, a multidisciplinary approach may be then necessary to decide the best treatment (i.e., direct oral anti-coagulants have not been approved for use in cases of cancer whereas cytoreductive drugs have

***Corresponding author:** Dr. Ianotto Jean-Christophe, Service d'Hématologie Clinique, Institut de Cancéro-Hématologie, Hôpital Morvan, Avenue Foch, CHRU de Brest, 29609 Brest cedex, France, Tel: 0033298223421; Fax: 0033298223323; E-mail: jean-christophe.ianotto@chu-brest.fr

Received April 25, 2017; **Accepted** May 15, 2017; **Published** May 22, 2017

Citation: Ianotto JC (2017) Screening for MPN Mutations in Cases of Deep Vein Thrombosis and/or Pulmonary Embolism: What We have learnt from Studies. Adv Tech Biol Med 5: 224. doi: 10.4172/2379-1764.1000224

been approved to reduce the risk of thrombotic recurrence in MPNs), screening for MPNs in these situation need to be discussed.

The purpose of this review is to analyze available data from studies referenced on PubMed website regarding only the screening of MPNs mutations in cases of DVT/PE, to summarize what we can learn from them and to propose an appropriate method for this screening, to reduce time and costs.

Results of Published Series on DVT/PE and MPNs Mutations Screening

Since 2005 when the JAK2V617F mutation was identified, sixteen studies of a series of patients have been published on this topic. Only two were related to the screening of CALR mutations and none addressed MPL mutations. All the results are listed in Table 1.

At least, 2907 patients have been screened for JAK2 or CALR mutations. Only 39 (1.3%) of these patients have been identified as being positive for JAK2. In cases that begin with idiopathic thrombosis, biologists identified only 27/2338 (1.15%) positive patients. In contrast, 12/569 (2.1%) patients with recurrent DVT/PE were identified as positive (in studies that clearly reported the recurrence status).

Unfortunately, of 394 patients with one thrombotic event and 372 patients with recurrence, none of the patients was positive for CALR mutations.

It may not be easy to determine the precise localization of venous events and the status of recurrence because the combination of DVT and PE was not systematically and clearly separated from DVT alone or PE alone. However, when this information was provided, the occurrence of DVT or PE did not change the prevalence of positivity. Additionally, the classification of an idiopathic event could also differ from one study to another, thus altering the rate of positivity.

Analyses of the Characteristics of the JAKV617F Positive Patients

Minimal data are available for 34 (87%) patients (Table 2). The sex ratio is 0.36 due to the presence of 25 women. The median age of the patients is 70 years (33-87), with 26 patients (76.5%) who are older than 60 years. From the hemogram, twelve (35.3%) patients had blood cell counts greater than the normal range (8 with leukocytosis, 6 with thrombocytosis and 2 with polycythemia). The median values were 9.3 giga/l (3.7-32.8) for leukocytes, 13.9 g/dl (8.9-17.7) for the hemoglobin level and 304 giga/l (154-1180) for platelets. The allele burden was quantified in 21 cases, with a median value of 3.4% (0.75-32). This level is low and more commonly associated with ET than with other MPNs [1].

Two patients were previously followed for MPNs at the time of their thrombosis and eight patients were secondary diagnosed as MPN (6 ET, 3 PV and 1 unspecified MPN) during the first year of follow-up. Interestingly, only patients with thrombocytosis or polycythemia were diagnosed for MPN (all but one with thrombocytosis). The occurrence of leukocytosis in some patients could only be related to the inflammatory state of the thrombosis (in most cases, the values spontaneously decrease into normal range). Thus, despite the presence of the JAK2V617F mutation, 70.6% of the patients failed to be diagnosed with MPN, even if the follow-up could be considered sufficiently long (median of 42 months, 0.25-112). Insufficient information has been obtained to determine whether these patients have been effectively seen by hematologists to confirm or rule out the MPN status.

Another interesting point is the recurrence rate: 19/28 (68%) of the patients who were positive for a JAK2 mutation experienced more than one thrombotic event regardless of the follow-up timing. Even if most of the patients did not exhibit MPN features, the presence of the JAK2V617F mutation could probably be considered as a thrombophilic state, which should not be minimized. These patients should be carefully followed once they are identified.

Resume and Comparison to other Thrombotic Sites Screening

For the first time, a complete analysis of published studies concerning the screening for MPNs mutations in case of DVT and/or PE has been made here. Salient points could be resumed as:

Authors	Years	Type of	Patients	JAK2 positive	CALR positive
		venous event	nb	cases-nb (%)	cases-nb
Colaizzo et al. [4]	2007	DVT	110	0	nd
Regina et al. [5]	2007	DVT and/or PE	44	0	nd
Remacha et al. [6]	2007	DVT	295	1 (0.3)	nd
Rossi et al. [7]	2007	DVT or PE	114	0	nd
Pardanani et al. [8]	2008	DVT and/or PE	196	2 (1)	nd
Sene et al. [9]	2008	DVT	38	0	nd
Ugo et al. [10] and Ianotto et al. [11]	2008 and 2016	DVT	394	6 (1.5)	0
Za et al. [12]	2009	DVT	194	2 (1)	nd
McCarthy et al. [13]	2010	DVT	81	3 (3.7)	nd
Shetty et al. [14]	2010	DVT	36	1 (2.7)	nd
Zerjavic et al. [15]	2010	DVT and/or PE	444	6 (1.4)	nd
Lauw et al. [16]	2012	DVT	178	4 (2.3)	nd
Linnemann et al. [17]	2012	DVT	93	1 (1.1)	nd
Moussaoui et al. [18]	2017	DVT	121	1 (0.8)	nd
Total			**2338**	**27 (1.15)**	**0**
Pardanani et al. [8]	2008	Recurrent VTE	197	2 (1)	nd
Ianotto et al. [19]	2017	Recurrent VTE	372	10 (2.7)	0
Total			**569**	**12 (2.1)**	**0**

Table 1: Screening for JAK2V617F and CALR mutations among patients who experienced idiopathic deep vein thrombosis and/or pulmonary embolism.
DVT: Deep Vein Thrombosis; nb: Number; nd: Not Done; PE: Pulmonary Embolism; VTE: Venous Thrombotic Event

Sex	Age	Leucocytes	Hemoglobin	Platelets	Allele burden	MPN	MPN	Follow-up	Venous
	(y)	(giga/L)	(g/dL)	(giga/L)	(%)	before	after	(m)	events
F	86	4.6	13.2	1180	2.5	ET	no	44	Recurr
F	73	10.9	17.7	305	25	PV	no	18	Recurr
F	65	7.6	14.7	559	2.5	no	PV	0.5	Recurr
M	69	nd	16.5	nd	nd	no	PV	nd	Recurr
F	78	15	12.3	537	2	no	ET	2	Recurr
F	63	7.8	13.1	594	2	no	ET	73	Recurr
F	66	11.7	12.7	449	20	no	ET	5	Recurr
F	33	nd	nd	nd	nd	no	ET	nd	Recurr
F	60	nd	nd	nd	nd	no	ET	nd	Recurr
F	49	nd	nd	nd	nd	no	uMPN	nd	Recurr
F	87	10.5	13.1	293	20	no	no	46	no
F	81	12.7	13.5	234	4	no	no	70	Recurr
M	51	10.5	8.9	375	4	no	no	42	no
F	87	17.3	13.9	297	32	no	no	3	Recurr
F	79	32.8	14.3	212	10	no	no	0.25	no
F	74	9.3	12.2	465	2.2	no	no	4	Recurr
M	63	8.2	14.6	265	15	no	no	22	Recurr
F	86	7.4	13.6	365	2.5	no	no	44	Recurr
F	73	9.9	14.9	265	2.5	no	no	112	Recurr
M	54	7.4	15.3	341	0.75	no	no	40	Recurr
M	56	8	15.4	279	1	no	no	35	Recurr
M	84	9,9	13.2	154	5.3	no	no	71	no
F	82	3.7	13.6	309	5	no	no	38	Recurr
M	69	8.9	14	361	9	no	no	60	no
F	71	nd	nd	nd	nd	nd	nd	nd	no
F	76	nd	nd	nd	nd	nd	nd	nd	no
F	40	9.4	14.2	294	nd	no	no	69	no
M	69	9.6	12.7	172	nd	no	no	85	no
M	43	5.5	16.3	277	nd	no	no	67	nd
F	85	7.7	15	304	0.87	no	no	47	nd
F	86	4.4	nd	205	2.8	no	no	30	nd
F	69	nd	nd	nd	nd	no	no	nd	nd
F	78	nd	nd	nd	nd	no	nd	nd	nd
F	53	nd	nd	nd	nd	no	nd	nd	nd
Median	**70**	**9.3**	**13.9**	**304**	**3.4**			**42**	

ET: Essential Thrombocythemia; F: Female; M: Male; m: Months; nd: Not Done; PV: Polycythemia Vera; uMPN: Unspecified Myeloproliferative Neoplasm

Table 2: Characteristics of the JAK2V617F-positive patients identified during the screening of DVT/PE occurrences.

1) Ten to fifteen percent of the MPNs diagnoses are made after a thrombotic event and one-third of the events are venous sites; 2) DVT and/or PE are the most frequent venous thrombotic sites in general population but the screening for MPNs mutations in these situations is unproductive with less than 1.5% of positivity; 3) a complete and systematical screening should be avoid in this thrombotic situation, in order to reduce costs and time wasting because only JAK2V617F have been found so, only patients with a proliferative profile on the hemograms should be screened to identify a MPN (<30% of the positive cases or 0.3% of all tested cases) enhancing the value of this simple and cheap exam; 4) all positive cases should be systematically investigated for MPN with a bone marrow trephine biopsy and/or red mass cells to change the way of treating them (systematical prescription of cytoreductive drugs); 5) but, even in case of non-proven MPNs, all the patients also need to be carefully followed to reduce thrombotic recurrence observed for 68% of them (i.e., long-lasting prescription of vitamin-K inhibitors like for patients with solid cancer ?).

The same analysis could be done for all thrombotic sites because most of them have been explored for MPNs mutations but, few data are available on the rare positive cases, reducing the value of this analysis. Far less frequent than DVT, thromboses of cerebral or retinal veins are also rarely found positives for JAK2V617F (5.2% and 0%, respectively), with no study for CALR mutations. Among arterial thrombotic events, only 0.6% of the screened patients were positive for JAK2V617F [20,21].

On the other hand, and despite their rarity, the most relevant sites to screen for MPNs mutations are splanchnic vein thromboses. In the principal published series, the authors have observed a positivity of JAK2V617F in 34% of portal vein thromboses and 47% of Budd-Chiari syndrome, but less than 1% of CALR positive cases [22]. Interestingly, in these thrombotic sites, most of the patients have normal blood counts due to a typical congestive splenomegaly. So, the patients with such an idiopathic thrombosis are the only ones who should be systematically investigated for MPNs mutations added to a bone marrow trephine biopsy (whatever was the results of the screening) and/or a red mass cells (in case of JAK2V617F positivity) to assess the presence of a MPN.

Conclusion

This review focused on the screening for classical MPN mutations among patients who experienced DVT and/or PE. This screening should not be systematically performed in these situations but only in case of thrombocytosis or polycythemia on hemograms and only for JAK2V617F mutation. All the positive cases should be discussed with hematologists after a bone marrow trephine biopsy to properly diagnose and treat a MPN.

References

1. Vainchenker W, Kralovics R (2017) Genetic basis and molecular pathophysiology of classical myelo-proliferative neoplasms. Blood 129: 667-679.
2. Tefferi A Barbui T (2017) Polycythemia vera and essential thrombocythemia: 2017 update on diagnosis, risk-stratification and management. Am J Hematol 92: 94-108.
3. Streiff MB, Agnelli G, Connors JM, Crowther M, Eichinger S, et al. (2016) Guidance for the treatment of deep vein thrombosis and pulmonary embolism. J Thromb Thrombolysis 41: 32-67.
4. Colaizzo D, Amitrano L, Iannaccone L, Vergura P, Cappucci F, et al (2007) Gain-of-function gene mutations and venous thromboembolism: Distinct roles in different clinical settings. J Med Genet 44: 412-416.
5. Regina S, Herault O, D'Alteroche L, Binet C, Gruel Y (2007) JAK2 V617F is specifically associated with idiopathic splanchnic vein thrombosis. J Thromb Haemost 5: 859-861.
6. Remacha AF, Estivill C, Sarda MP, Mateo J, Souto JC, et al. (2007) The V617F mutation of JAK2 is very uncommon in patients with thrombosis. Haematologica 92: 285-286.
7. Rossi D, Cresta S, Destro T, Vendramin C, Bocchetta S, et al (2007) JAK2V617F in idiopathic venous thromboembolism occurring in the absence of inherited or acquired thrombophilia. Br J Haematol 138: 813-814.
8. Pardanani A, Lasho TL, Hussein K, Schwager SM, Finke CM, et al (2008) JAK2V617F mutation screening as part of the hypercoagulable work-up in the absence of splanchnic venous thrombosis or overt myeloproliferative neoplasm: Assessment of value in a series of 664 consecutive patients. Mayo Clin Proc 83: 457-459.
9. Sène D, Elalamy I, Ancri A, Cacoub P (2008) JAK2V617F mutation is not associated with unexplained recurrent arterial and venous thrombosis. Thromb Res 122: 427-428.
10. Ugo V, Le Gal G, Lecucq L, Mottier D, Oger E, et al. (2008) Prevalence of the JAK2 V617F mutation is low among unselected patients with a first episode of unprovoked venous thromboembolism. J Thromb Haemost 6: 203-205.
11. Ianotto JC, Chauveau A, Luque PD, Delluc A, Tromeur C, et al. (2016) Absence of CALR mutation among a cohort of 394 unselected patients with a first episode of unprovoked venous thromboembolism. Thromb Haemost 115: 225-226.
12. Za T, Fiorini A, Rossi E, Ciminello A, Chiusolo P, et al. (2009) Prevalence of the JAK2 V617F mutation in patients with unprovoked venous thromboembolism of common sites and without overt myeloproliferative neoplasms. Br J Haematol 144: 965-967.
13. McCarthy N, McCarron SL, Langabeer SE (2010) Prevalence of the JAK2 V617F and MPL mutations in stroke, abdominal and peripheral venous thrombosis. Acta Haematol 124: 160-161.
14. Shetty S, Kulkarni B, Pai N, Mukundan P, Kasatkar P, et al. (2010) JAK2 mutations across a spectrum of venous thrombosis cases. Am J Clin Pathol 134: 82-85.
15. Zerjavic K, Zagradisnik B, Stangler HS, Lokar L, Glaser KM, et al. (2010) Is the JAK2 V617F mutation a hallmark for different forms of thrombosis? Acta Haematol 124: 49-56.
16. Lauw MN, Bus EW, van Wulffften PAF, Coppens M, Homburg CH, et al. (2012) Relevance of the JAK2V617F mutation in patients with deep vein thrombosis of the leg. Ann Hematol 91: 103-107.
17. Linnemann B, Kraft C, Roskos M, Zgouras D, Lindhoff-Last E (2012) Inferior vena cava thrombosis and its relationship with the JAK2V617F mutation and chronic myeloproliferative disease. Thromb Res 129: 720-724.
18. Moussaoui S, Saussoy P, Ambroise J, Defour JP, Zouitene R, et al. (2017) Genetic risk factors of venous thromboembolism in the East Algerian population. Clin Appl Thromb Hemost 23: 105-115.
19. Ianotto JC, Chauveau A, Mottier D, Ugo V, Berthou C, et al (2017) JAK2V617F and calreticulin mutations in recurrent venous thromboembolism: Results from the EDITH prospective cohort. Ann Hematol 96: 383-386.
20. Xavier SG, Gadelha T, Rezende SM, Zalcberg IR, Spector N (2011) JAK2V617F mutation in patients with thrombosis: To screen or not to screen? Int J Lab Hematol 33: 117-124.
21. Casini A, Fontana P, Lecompte TP (2013) Thrombotic complications of myeloproliferative neoplasms: Risk assessment and risk-guided management. J Thromb Haemost 11: 1215-1227.
22. Kiladjian JJ, Cervantes F, Leebeek FW, Marzac C, Cassinat B, et al. (2008) The impact of JAK2 and MPL mutations on diagnosis and prognosis of splanchnic vein thrombosis: A report on 241 cases. Blood 111: 4922-4929.