Editorial

Splanchnic vein thrombosis in myeloproliferative neoplasms: facing the opposite risks of thrombosis recurrence and bleeding

Massimo Primignani, Giulia Tosetti

Gastroenterology and Hepatology Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

Correspondence to: Massimo Primignani. Gastroenterology and Hepatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, via Sforza 35, Milano 20122, Italy. Email: massimo.primignani@policlinico.mi.it.

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Introduction

The article "*Splanchnic vein thrombosis in myeloproliferative neoplasms: risk factors for recurrences in a cohort of 181 patients*", recently published in the *Blood Cancer* Journal (1), retrospectively addresses the issue of thrombotic recurrence in patients with Philadelphia-negative myeloproliferative neoplasms (MPN), after a first episode of splanchnic vein thrombosis (SVT).

Twenty-three centres of the European Leukaemia Network selected from their patients with MPN those who had had SVT, either as the signalling manifestation of MPN or later on in the course of the disease, and had received anticoagulation, mainly with vitamin K antagonists (VKA).

The following paragraphs present a short synopsis of the study.

The collected data included demographics, WHO diagnosis, site of thrombosis, occurrence of microvascular or constitutional symptoms, mutational profile, results of the thrombophilia screening, full blood count at diagnosis and at the time of thrombosis, and the presence of cardiovascular risk factors (previous thrombosis before the index event, smoking habit, hypertension, dyslipidemia and diabetes). In addition, the occurrence of circumstantial risk factors at the time of thrombosis, such as surgery, pregnancy or puerperium, oral contraceptive intake or hormone replacement therapy, trauma, prolonged bed immobilization and long travel as well as data on cytoreductive or antithrombotic treatment after VTE, duration of treatment and reasons for its withdrawal were collected.

A multivariable model, including age >60 years, thrombosis history, cardiovascular risk factors, haemoglobin >15 g/dL, haematocrit >45%, white blood cell count $>14\times10^9$/L, platelet count $>500\times10^9$/L, splenomegaly, unprovoked event, BCS versus other SVT as index event, VKA and other treatments, was performed to identify the predictors of thrombosis recurrence or bleeding.

Overall, 181 patients with SVT occurring at MPN diagnosis (58%) or during the course of the disease were recruited. The female sex was prevalent (65.2%); at the time of the index event, only a minority of patients (22.1%) were over 60 years of age. Budd-Chiari syndrome and portal vein thrombosis were diagnosed in 31 and 109 patients, respectively, whereas 41 patients had isolated thrombosis of the mesenteric or splenic veins. Most patients had splenomegaly and one quarter had microvascular disturbances and constitutional symptoms. Almost all carried the JAK2V617F mutation and 35% had genetic or acquired thrombophilia. SVT was unprovoked in most patients. Of note, more than 60% of patients had elevated blood counts, defined as Hct >45% and/or WBC $>14\times10^9$/L and/or platelet count $>500\times10^9$/L.

The study results show that the rate of recurrent thrombosis in MPN patients with SVT as index event is only reduced, and not completely prevented, by VKA. Actually, in front of a recurrence rate of 7.2 per 100 patient-years in untreated patients , those receiving VKA still had a recurrent rate of 3.9 per 100 patient-years, which is lower but still disappointingly high. The risk factors significantly associated with recurrence of thrombosis at multivariable analysis were: type of SVT (i.e., Budd-Chiari

versus other SVT), history of thrombosis, splenomegaly and leucocytosis. Major bleeding, either intracranial or extracranial, occurred mainly in patients on VKA and the corresponding rate was 2.0 per 100 patient-years.

Such results lead to the conclusion that the thrombosis recurrence rate after SVT in MPN is high, despite VKA treatment, thus suggesting that new modalities of prophylaxis of thrombosis recurrence, i.e., with new antithrombotic drugs and/or JAK-2 inhibitors should be explored in future studies.

Comment

MPN are associated with an increased risk of arterial and venous thrombosis.

Age, thrombosis history, smoking, hypertension, diabetes, leukocytosis, inflammatory markers and the presence of the gain-of-function JAK2V617F (JAK-2) mutation have been identified as risk factors for thrombosis in these patients, although considerable heterogeneity of data exists (2-4).

The occurrence of SVT, occurring either as the heralding presentation of MPN or as a complication during the course of the disease, poses additional problems to the clinician, as high risk of severe thrombosis recurrence and high risk of bleeding, either intrinsically linked to anticoagulation or due to portal hypertension (and potentially heightened by anticoagulation) coexist (5).

Facing opposite risks: thrombosis recurrence and bleeding

SVT, if not promptly diagnosed and successfully counteracted, may result in portal hypertension and the development of esophageal and/or gastric varices. Such changes involve a significant risk of severe gastrointestinal bleeding, often perceived by clinicians as a contraindication to anticoagulation, particularly if long-term treatment is advisable. Likewise, the risk of thrombosis recurrence is also unacceptably high in patients with MPN and the related high morbidity and mortality strongly argues in favour of long-term anticoagulation. Overall, taking into account the severity of SVT recurrence or progression and the comparatively lower mortality of portal hypertensive bleeding in such patients with SVT but without cirrhosis, current guidelines support long-term anticoagulation, provided that portal hypertensive bleeding is prevented, following the guidelines recommended for cirrhosis (6).

Indeed, in the study by De Stefano *et al.* (1) such recommendations were acknowledged, since as many as 85% of patients were treated with VKA and nearly 90% of them were on long-term treatment. Unfortunately, the study shows that thrombosis recurrence is only reduced, but not completely prevented by VKA. In fact, in front of a recurrence rate of 7.2 per 100 patient-years in patients untreated with VKA, those receiving VKA still had a recurrent rate of 3.9 per 100 patient-years, lower but still disappointingly high, and these recurrences occurred mainly at the splanchnic level. Such results are not surprising as VKA, also in the setting of preventing thrombosis recurrence of the lower limbs, showed a lesser benefit in MPN than in non-MPN patients, thus signifying a higher thrombotic potential in the former group (7).

It is noteworthy that the international normalized ratio (INR) at the time of recurrence, available in 13 cases, was within the therapeutic range only in six, and below or beyond it in five and two cases, respectively. Such findings highlight the possible benefits that direct oral anticoagulants (DOACs), through a more predictable anticoagulant effect, could have on the risk of venous thrombosis recurrence. DOACs are increasingly used in patients with SVT, many of them affected with MPN, but experience is still limited and data from controlled studies allowing a comparison between patients treated with DOACs or with traditional anticoagulants lacks. Although preliminary data is encouraging (8), whether DOACs could decrease the rate of recurrent venous thrombosis better and with a better safety profile than VKA remain unsettled.

Facing arterial thrombosis risk

A second issue refers to the arterial thrombosis recurrences. Whether VKA could prevent also arterial thromboses after a venous thromboembolism is unclear. The study by De Stefano *et al.* (1) could not demonstrate an extra benefit of combining aspirin and VKA, but the number of treated patients was too small to allow meaningful conclusions. In fact, ten thromboses recurred at the arterial site, with an overall incidence rate of 1.3 per 100 patient-years. Only ten patients received aspirin in association with VKA and such combination did not translate into a significant advantage on the overall thrombosis rate. However, it is noteworthy that all the arterial thrombosis events occurred in the absence of antiplatelet agents. Therefore, VKA are less effective in preventing recurrent arterial thromboses in MPN patients, but aspirin seems to be effective, although these conclusions rely on a limited number of observations. However, data on the beneficial effect of aspirin in preventing arterial disease

in MPN patients is solid. Treatment with low-dose aspirin was associated with decreased risk of the combined end-point of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes in a trial including 518 patients with polycythemia vera (9). Also in essential trombocytemia, despite the lack of data from randomized studies, aspirin reduced microvascular symptoms (10). Nonetheless, several reasons suggest caution with the use of aspirin (and/or other antiplatelet agents) to prevent arterial thrombosis in MPN patients with SVT and portal hypertension. In fact, in such setting, combining aspirin with VKA could cause an excessively high bleeding rate.

Our knowledge on the adverse events associated with aspirin use in patients with portal hypertension stems mostly from studies in cirrhosis patients. Indeed, in patients with esophageal varices, aspirin use was associated with an increased risk of variceal bleeding (11). Conversely, aspirin was relatively safe in cirrhosis patients without significant varices after coronary artery stenting (12). The same concerns apply to the use of P2Y12 inhibitors, which block ADP-induced platelet aggregation, at least in patients with esophageal varices. Indeed, the rate of variceal bleeding in cirrhosis patients with esophageal varices receiving antiplatelet agents following stent placement is substantial (but whether such increased risk also extend to portal hypertension due to SVT in MPN patients is another unsettled item).

Overall, taking into account advantages and concerns, caution with combining VKA and aspirin should prevail, at present, in the setting of MPN with SVT and portal hypertension. Indeed, a retrospective study involving MPN patients with previous thrombosis events showed that either antiplatelet agents or VKA reduced thrombosis recurrence with acceptable safety, whereas the combination therapy increased the rate of major bleeding compared with antiplatelet agents or VKA alone (2.8 per 100 versus 0.8 per 100 and 0.9 per 100 patient-years, respectively). Therefore, and particularly in the setting of portal hypertension, it is likely that VKA plus aspirin could increase the hemorrhagic risk. At present, the issue of aspirin and/or other anti-platelet drugs as an add-on antithrombotic treatment in MPN patients with SVT is included in the research agenda for future studies in the recent Baveno VI consensus (6).

Does cytoreduction decreases the thrombotic risk?

A third issue refers to the impact of cytoreduction on the risk of thrombosis recurrence. In the study by De Stefano *et al.* (1), cytoreduction (hydroxyurea in most cases) was administered to 130 of 181 patients (72% of the cohort), combined with VKA in 107. There were no differences in the type of MPN, age over 60 years, BCS as index event, increased peripheral blood counts, splenomegaly and VKA treatment in patients receiving or not cytoreduction. The retrospective nature of the study and the absence of a scheduled indication to cytoreduction accounts for these findings. Taking into account these limitations, the incidence rate of recurrent thrombosis was similar in patients receiving cytoreduction or not (4.2 per 100 versus 4.0 per 100 patient-years, respectively). Whether these disappointing results suggest little or no role for cytoreduction in preventing thrombosis recurrence is however questionable, as more than half of thrombosis recurrences occurred in patients with hypercythaemia not receiving cytoreduction or in patients who failed to reach the hematological response in spite of cytoreduction. Moreover, keeping values of Hb >15 g/dL, or WBC count $>14\times10^9$/L, or platelet count $>500\times10^9$/L as indicative of poor control of blood cell proliferation may be appropriate for patients without portal hypertension, but is probably inadequate for patients with portal hypertension. Indeed, in patients with MPN complicated by SVT and portal hypertension, plasma volume expansion, further increase of spleen size and occult or overt blood losses tend to decrease the peripheral blood counts, without affecting the proliferation rate of blood cells, which is responsible for the thrombotic risk. Although no consensus exist on the blood cell count to achieve with cytoreduction in patients with MPN and portal hypertension due to SVT, many experts suggest targeting the platelet count around 200×10^9/L.

The issue of the prevention of thrombosis recurrence was also retrospectively addressed in 494 MPN patients with previous venous thrombosis at usual sites (13). Again, the finding that two-thirds of recurrent thromboses occurred in patients with hypercythaemia suggested the potential benefits of cytoreduction. Conversely, since many patients receiving cytoreduction did not reach a good control of blood cell proliferation, cytoreductive treatment did not translate into a significant reduction of venous thrombosis recurrence. Overall, the issue of the impact of cytoreduction on the risk of thrombosis recurrence is still unsettled.

Need for laboratory markers of thrombosis risk. Have we got them?

Undoubtedly, subjects with MPN have a high thrombosis

risk but, particularly in those developing portal hypertension due to SVT, also a severe bleeding risk must be accounted for, both intrinsically linked to MPN and further increased by portal hypertension and anticoagulation. However, the thrombosis concern should prevail because of the life-threatening impact of SVT recurrence. Certainly, an accurate assessment of the thrombotic risk in the single patient, if available, could help in personalizing a treatment strategy able to minimize both risks, providing highly effective anti-thrombotic treatments to high-risk patients, and deserving less intensive treatments to patients at lower risk, thus limiting the occurrence of bleeding events. Although age, thrombosis history, leucocytosis and the JAK2V617F mutation increase the thrombosis risk, such factors were not differently represented in the study cohort and could not help identifying those with recurrent thrombosis. Also thrombophilia, both inherited and acquired, although investigated and recognized in 35% of cases, could not add discriminative capacity in identifying thrombosis relapses.

Therefore, the question is whether other laboratory markers of thrombosis risk could help in this clinical scenario. Do they exist? In a recent study (14), global coagulation tests such as thrombin generation in platelet-rich plasma (with platelet count adjusted to the original patient count) or thromboelastometry in whole blood were able to detect signs of procoagulant imbalance in MPN as compared to controls. The endogenous thrombin potential (ETP) was performed with and without thrombomodulin (the physiological protein C activator) and results were expressed as ETP ratios (with/without thrombomodulin). High ETP ratios reflect resistance to thrombomodulin and designate procoagulant imbalance. ETP ratios were higher in patients than in controls and were directly correlated with platelet counts and inversely with the plasma levels of free protein S, protein C and antithrombin. Concerning thromboelastometry, some parameters of the test as a short clot formation time (CFT) or a high maximal clot firmness (MCF) also designate procoagulant imbalance. Indeed, CFT was shorter and MCF was greater in MPN patients than controls. Therefore, it appears that either the ETP ratio or thromboelastometry are able to detect the procoagulant imbalance occurring in MPN patients. In addition, high levels of platelet and endothelial-derived microparticles have been described in MPN patients and may play a pathophysiologic role in thrombosis (15). However, whether these tests might help in stratifying the thrombosis risk of MPN patients deserve a proper assessment in future studies.

A further issue is whether laboratory test could measure the impact of cytoreduction on the procoagulant imbalance in MPN. Indeed, a recent study (16) showed that hydroxyurea, alone or in combination with antiplatelet drugs, decreased the ETP ratio to values approaching those of the control population and that such normalization paralleled the reduced release of circulating microparticles exposing phosphatidylserine with procoagulant activity induced by hydroxyurea. Such study seems to confirm that the ETP ratio not only reflects the procoagulant imbalance in MPN, but also measures its changes induced by cytoreductive treatment.

Whether the decrease of the procoagulant imbalance translates into a decreased rate of thrombosis in MPN patients treated with hydroxyurea or other drugs as the JAK2/JAK1 inhibitor ruxolitinib is still unknown. However, it appears that the ETP ratio (and perhaps thromboelastometry) could be valuable tools to assess the thrombotic risk and to monitor its time changes possibly induced by treatments, in order to adjust anticoagulation to the patient's requirements. Whether such guess is valid deserves a proper assessment in the frame of clinical trials.

Conclusive remarks

In summary, the opposite issues of thrombotic and hemorrhagic risk in patients with MPN and previous SVT represent a clinical challenge, as the indication to long-term anticoagulation to prevent thrombosis recurrence must also take into account the bleeding risk due to portal hypertension. Whether cytoreduction is able to abate the thrombosis risk, although biologically plausible and supported by laboratory tests, is not clinically proven, and the study by De Stefano *et al.* (1) could not corroborate such hypothesis, since an adequate control of cell proliferation was not achieved in many patients enrolled in the study. Therefore, the question is still unanswered. Long-term anticoagulation with VKA, although required to prevent recurrent thrombosis, is not able to fully prevent it and entails a substantial hemorrhagic risk, particularly in portal hypertensive patients. Whether DOACs will better prevent thrombosis recurrence with a better safety profile is possible, but still unsettled. Finally, further studies will clarify whether a tailored therapeutic approach to the thrombosis risk of MPN patients, taking into account both clinical and laboratory tests suggestive of procoagulant imbalance, will minimize both the thrombosis recurrence

rate and the bleeding risk.

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