Pathogenesis and management of thrombotic disease in myeloproliferative neoplasms

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Abstract

Chronic myeloproliferative neoplasms (MPN) are characterized by clonal expansion of an abnormal hematopoietic stem/progenitor cell and include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Venous thrombosis, often at unusual sites including splanchnic vein thrombosis and arterial thrombosis as well as a hemorrhagic tendency and a propensity to transform into myelofibrosis or acute leukemia are common complications in patients with MPNs. The pathogenesis of thrombosis in MPN patients is complex and multifactorial. Disease related factors such as an increase in blood cell counts (ie, leukocytosis, erythrocytosis, and thrombocytosis) and more importantly presence of JAK2 mutation can interact with non-disease patient related factors age, previous history of thrombotic events, obesity, hypertension, hyperlipidemia, and presence of thrombophilic defects. The overall rate of recurrent thrombosis after venous thromboembolism (VTE) is 6.0 to 6.5 per 100 patient-years in patients with MPN compared to 2.7 - 3.7 per 100 patient-years in patients without MPN, and antithrombotic therapy with vitamin K antagonists (VKAs) is associated with a clear benefit, reducing the incidence of recurrence by 48 to 69%. Life-long oral anticoagulation with VKAs is the cornerstone of the antithrombotic treatment for splanchnic vein thrombosis (SVT). Patients with MPN-related cerebral venous thrombosis (CVT) should also be treated with long-term anticoagulation with VKAs. The role of direct acting oral anticoagulants in patients with thrombosis and MPN is not established and the use of these anticoagulants should be considered on an individual basis according to the risk of recurrent of VTE and bleeding.

Key words: Polycythemia vera, Essential thrombocythemia, Thrombosis, Anticoagulation, Antiplatelet treatment

Introduction

Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are chronic myeloproliferative neoplasms (MPN) characterized by clonal expansion of an abnormal hematopoietic stem/progenitor cell. Their clinical course is characterized by both thrombotic and hemorrhagic complications and a tendency to transform into myelofibrosis and acute leukemia. Diagnosis of MPN and understanding of their pathophysiology improved significantly following the identification of recurrent molecular abnormalities, primarily the V617F mutation in JAK2 exon 14, which is found in 95% of PV and; 60% to 70% of ET and PMF patients [1]. Although there is a strong association between MPN and thrombosis of both venous and arterial systems, many general practice physicians fail to identify the link between MPN and thrombosis. Thrombosis associated with MPN can be anywhere in the venous or arterial systems but particularly in unusual sites such as cerebral venous thrombosis (CVT) and splanchnic vein thrombosis (SVT) which includes portal vein (PVT), mesenteric (MVT) and splenic vein thrombosis, and the Budd–Chiari syndrome (BCS). When these present without obvious local pathology they should be investigated for the molecular abnormalities associated with MPN. Some patients develop thrombosis, especially SVT, associated with the JAK2 mutation but with a completely normal full blood count. Isolated JAK2 mutations occur in approximately 0.1% to 0.2% of the general population, and a myeloproliferative phenotype can develop in individuals bearing this allele over a period of 4 or 5 years [2]. Patients presenting with thrombosis at more usual sites such as deep vein thrombosis (DVT) and pulmonary embolism (PE) or with arterial thrombosis should be investigated for an underlying MPN if they have elevated hemoglobin [Hb] or hematocrit (Hb >165 g/L in men and >160 g/L in women or Hct > 0.49 in men and >0.48 in women) or a platelet count ≥450 X 109/L, as defined by the revised 2016 WHO criteria [2].

The aim of this review is to consider the pathogenesis and management of thrombosis, both venous and arterial thrombosis in patients with MPN.

Incidence and types of thrombosis

The European Collaboration on Low-dose Aspirin (ECLAP) is the largest epidemiologic study of PV to date and in this study, thrombosis accounted for 41% of all deaths (1.5 deaths per 100 persons per year), mainly due to coronary heart disease (25% of all deaths), congestive heart failure (13%), non-hemorrhagic stroke (13%), and pulmonary embolism (6%) [3]. This incidence is much higher than that of the general population, in whom the annual incidence of major VTE is between 0.1 and 0.2% per annum.[4]. Many patients with a previous history of thrombosis were found to have had abnormal blood counts at presentation with thrombosis, suggesting that some patients may have a delayed diagnosis of MPN due to failure to recognize the link between MPN and thrombosis. There is some variation in reported incidence figures for major thrombosis at diagnosis that range from 9.7 to 29.4% for ET and 34 to 38.6% for PV; the corresponding figures for major thrombosis during follow-up are 8 to 30.7% for ET and 8.1 to 19% for PV. In almost all instances, arterial events were more prevalent than venous events, and thrombosis in general was more frequent than major bleeding [5].

Arterial thrombosis, which accounts for 60%-70% of thrombotic events related to MPNs, includes ischemic stroke, transient ischemic attack (TIA), angina, acute myocardial infarction, and peripheral arterial occlusion which can present as ischemia/intermittent claudication and or digital gangrene[6]. Presenting symptoms of small vessel thrombosis in MPN can vary and may include mental concentration disturbances followed by throbbing headaches, nausea, vomiting, syncope or even seizures [6]. In addition, microvascular ischemic and thrombotic complications such as erythromelalgia, peripheral paresthesia, migraine-like headache transient ischemic attacks, visual or hearing transitory defects can dominate the clinical picture at presentation of MPN. These symptoms often respond to control of

platelet function with low dose aspirin (LDA)[7]. Venous thrombosis can present as thrombosis at usual sites such as DVT, PE, or thrombosis at unusual sites such as SVT including the BCS. The prevalence of SVT and cerebral vein thrombosis is unusually high among patients with MPN accounting for approximately 50% of BCS and 25% of portal vein thromboses (PVT)[8] cases. If recurrent thrombosis occurs, it is most frequently in the previous distribution of thrombosis (arterial vs venous). However, around 1/3 of the patients with VTE can have recurrence in the arterial circulation and vice versa[9]. In patients presenting with SVT, even in patients with a MPN phenotype on bone marrow assessment can have normal or lower blood counts, which is most likely due to hepatosplenomegaly.[8]

Pathogenesis of thrombosis in MPN

The pathogenesis of thrombosis in MPN patients is complex and multifactorial. Disease related factors such as increase in blood cell counts (i.e., leukocytosis, erythrocytosis, and thrombocytosis) and more importantly presence of JAK2 mutation can interact with non-disease patient related factors such as age, previous history of thrombotic events, obesity, hypertension, hyperlipidemia, genetic traits such as factor V Leiden, prothrombin gene mutations and use of combined oral contraceptive pills or estrogen containing hormone replacement therapy resulting in increased risk of thrombosis. However, routine testing for inherited or acquired thrombophilia is not recommended in patients with MPN since this will not change the management [10].

In the ECLAP study, age ≥65 years and a prior history of thrombosis were found to be the most important predictors of cardiovascular events [3]. These factors have consistently proven to be independent predictors of future events in PV, ET, and PMF. A base-line white blood cell (WBC) count of >15x 10^9/L was a significant predictor of thrombosis, particularly an increased risk of myocardial infarction [3]. Once treatment is initiated for PV, cardiovascular events occur more frequently in patients with poor hematocrit control and when the WBC count remains elevated >11 × 10^9/L[11]. A relationship

between platelet count (either at diagnosis or follow-up) and thrombotic risk has not been established in PV, but severe thrombocytosis (≥1500 × 10^9/L) is associated with increased risk of bleeding due to acquired von Willebrand disease and should be considered an indication for cytoreductive therapy [1,11].

A hallmark of patients presenting with MPN related thrombosis is presence of the JAK2 (V617F) mutation, which has a strong link with thrombosis in both venous and arterial systems. The JAK2 (V617F) mutation is present in 95% of patients with PV and around 60% patients with ET or PMF. JAK2 exon 12 somatic mutation is found in most of the remaining 5% of patients with PV. Mutations of MPL exon 10 are present in about 5 % of those with ET or PMF[12-14]. In patients without JAK2 or MPL mutation, 67%–71% of those with ET and 56%–88% of those with MF are found to be positive for calreticulin gene (CALR) mutation[15]. In a study by Rumi et al, of 1235 consecutive patients diagnosed with ET or PV, the incidence of thrombosis associated with JAK2-mutated patients with ET and PV was similar; 7.1% and 10.5% respectively and was twice that of patients with the CALR mutated patients with ET (2.8%). The incidence of thrombosis associated with JAK2 exon 12 and MPL mutations are not well documented due to the small number of patients with these mutations.

It has been shown that JAK2 mutation can lead to structural and functional abnormalities in all three hematological cell lines (red blood cells, white blood cells and platelets) as well as endothelial cells, which leads to increased cell aggregation and binding and activation of the endothelium causing increased risk of thrombosis[10]. JAK2V617F-expressing endothelial cells can promote thrombosis through induction of endothelial P-selectin expression, which can be reversed by hydroxyurea [16].

In addition, activated blood cells express procoagulant and proteolytic properties, secrete inflammatory cytokines and express adhesion molecules, which together contribute to thrombosis. Activated platelets express P-selectin and tissue factor (TF) and release microparticles. The increased expression of CD11b on the neutrophil surface allows the adhesion of neutrophils to endothelial cells and platelets.

Abnormalities in red blood cells, including biochemical changes in the cell membrane and content, may independently impair blood flow as well, through the formation of red cell aggregates[10]. Furthermore, red cell aggregation facilitates platelet and leukocyte interaction with the vessel wall. Figure 1 summaries the mechanisms in which MPN can increase the thrombotic risk through cell activation and inflammation. Mechanisms of thrombosis may be related to rheologic factors. Rheological characteristics of blood are primarily determined by the hematocrit (Hct), the properties of red cells and their interaction with each other as well as with the surrounding structures including fibrinogen[17]. In large vessels, viscosity increases exponentially with Hct which may explain the increase in cardiovascular risk observed with relatively small increases in Hct. Observations that Hct correlates positively with vascular occlusive episodes led to the adoption of current clinical guidelines to maintain PV patients at Hct <0.45[1]. Accordingly, the CYTO-PV trial showed that therapeutic phlebotomy to maintain Hct <0.45 is associated with a thrombosis risk nearly fourfold lower than that of patients with hematocrits between 0.45 and 0.50 [18]. Patients with secondary erythrocytosis who are symptomatic because of hyper-viscosity or have a Hct > 0.56 should be considered for venesection to reduce this to 0.50-0.52 [10]. The risk for thrombosis in patients with JAK2 V617F mutation is at least twice higher compared to patients with CALR mutation [19]. Differences in the thrombotic risk in patients with CALR mutations and JAK 2 mutated patients are most likely explained by the fact that patients with CALR mutation have been reported to have an earlier disease[10] onset, higher platelet count but lower white blood cell count and hemoglobin level compared with those with JAK2 V617F[20]. In addition, the ability of JAK2 V617F to cause functional and structural changes of all three cell lines and the endothelial cells favoring thrombosis, raised red cell count/Hct and white in patients with JAK2 mutation compared to patients with CALR mutation also can further increase the risk of thrombosis as explained earlier.

Primary prophylaxis for prevention of thrombosis in MPN

Primary prevention focusses on interventions to reduce the risk of developing thrombosis and bleeding. Given the high mortality associated with thrombotic events in patients with PV, the first goal of therapy is to reduce the risk of thrombosis, which is achieved mainly by controlling Hct to < 0.45 [1]. However, frequent venesection in PV patients should be done with caution as it can cause thrombocytosis secondary to iron deficiency. Combined cytoreduction and periodic venesection can be used overcome this complication. Thus, in addition to venesection, cytoreduction with hydroxycarbamide (hydroxyurea, anagrelide, interferon alfa, ruxolitinib (which is a JAK2 inhibitor) should be considered especially in high risk category patients; defined as those ≥60 years old and/or those with a history of thrombosis[1;10]. Management should ensure in addition to keeping a stable Hct (<0.45), white blood cells and neutrophils are maintained in the normal range, and platelets <400 x109/L[1;10].

In addition to control of Hct, white cells and platelets counts, primary prevention of thrombosis should address adequate control of cardiovascular risk factors such as hypertension, high cholesterol, diabetes mellitus and stopping smoking. As the risk stratification systems use age ≥ 60 years as the high-risk category in MPN, this is already built into many health care systems, which require annual assessment and treatment of cardiovascular risk factors in these patients. Patients aged 40 to 60 years with MPNs categorized as intermediate or low risk depending additional risk factors, are not included in these routine risk assessments in most national healthcare systems. This should be highlighted to primary care physicians and vascular comorbidities should be kept under review. An annual review of vascular risk status should be undertaken, and treatment should be escalated if required [1]. Better control of risk factors such as smoking, blood sugar and hyperlipidemia and ensuring adherence to the prescribed drugs (antithrombotic, anti-hypertensive, statins, and antidiabetics) are important.

The benefit of LDA in patients with PV in primary prevention of thrombosis was demonstrated in the ECLAP study[21]. In this study it was found that LDA (aspirin 100 mg) daily resulted in significantly lower thrombotic events at 3 years compared to placebo[21]. Following this study, LDA is recommended and

should be started as soon as the diagnosis is made for the primary prevention of thrombosis in patients with PV or ET unless there is a contraindication or significantly high platelet count[1;21]. Although the dose of aspirin used varied across studies, 75 to 100 mg/day is commonly used. Aspirin should be avoided in patients with extreme thrombocytosis (e.g platelet count ≥1500 x 10^9/L) due to increased risk of bleeding as a result of acquired von Willebrand disease (AVWD) [1]. The term AVWD is used to describe a condition caused by acquired reduction in von Willebrand factor function, which in MPN is most likely due to increased binding of VWF to platelets, promoting cleavage by ADAMTS13 [22]. Diagnosis of AVWD is made by detection of reduced VWF:RCo/Ag ratio of <0.6–0.7 and loss of HMW multimers[23] as seen in patients with type 2 von Willebrand disease . Therefore, those with extreme thrombocytosis or elderly patients with high platelet count should have cytoreductive treatment first to bring down the platelet count prior to starting LDA due to greater risk for mortality and morbidity from bleeding than from thrombosis. Low-risk patients with ET (patients <40 years of age with no additional high-risk features) and patients with CALR mutation may not receive any benefit from LDA and have been reported to have a higher rate of complications from bleeding. Patients with a previous history of VTE prior to diagnosis of MPN, should be anticoagulated with a vitamin K antagonist (VKA) such as warfarin rather than giving aspirin due to high risk of recurrent VTE in the absence of anticoagulation[1].

In patients with primary myelofibrosis (PMF), although the incidence of thrombotic events is higher than the general population, it is lower than patients with PV and ET. In a retrospective single center study of 155 patients with PMF showed that incidence of VTE was significantly more frequent than in the general population (odds ratio [OR] 17.5; 95% confidence interval [CI] 10.3–31.4)[24]. Another larger retrospective multicenter study with 707 patients with WHO-defined MF, showed an incidence of fatal and non-fatal thrombotic events of 1.75 per 100 patient-years[25]. However, thrombocytopenia is a common manifestation of the disease and the overall risk for thrombosis is overtaken by leukemic transformation. In addition, splenomegaly and the use of the JAK inhibitor ruxolitinib (Jakafi, Incyte) also

contributes to thrombocytopenia and increased bleeding, necessitating caution with the use of aspirin in these patients[9]. Therefore, primary thromboprophylaxis with LDA usually is not routinely recommended for patients myelofibrosis only for a selected group of patients with additional cardiovascular risk factors paying careful attention to bleeding and thrombocytopenia[9]. Pre-operative planning for MPN patients undergoing surgery should involve review by a hematologist to optimize blood count and Hct control and to personalise the peri-operative plan[10], For patients with MPN and no previous history of VTE, after optimizing the blood count, standard antithrombotic prophylaxis is recommended [10].

Management of acute thrombosis and subsequent management at usual sites

Management of acute thrombosis and long-term management venous thrombosis at usual sites such as DVT of legs or PE in MPN patients should be the same as DVT or PE occurring in the non-MPN patients except that the role of direct acting oral anticoagulant in these patients especially those with high risk has not been established. Therefore, low-molecular-weight heparin (LMWH) with early initiation of VKA aiming to target an international normalized ratio (INR) of 2.5 (range 2.0–3.0) is recommended [9]. LDA should be stopped when anticoagulation is started due to increased risk of bleeding in majority of patients. Continuation of antiplatelet treatment with anticoagulant should be only in selected patients based on their risk of recurrent thrombosis vs bleeding.

Unlike management of venous thrombosis, where anticoagulation is the main modality of treatment, treatment of arterial thrombosis less clear. Patients with arterial thrombosis usually treated with antiplatelet treatment with LDA or ADP-receptor antagonist, clopidogrel or both. However, the role of clopidogrel, in the long-term prevention of MPN related arterial thrombosis has not been investigated. If a patient develops VTE despite being on primary prophylaxis with LDA, in addition to starting anticoagulant treatment with LMWH followed by VKA, cytoreductive treatment to control the blood

count should also be instituted. If a patient develops new or recurrent arterial event despite being on LDA once daily, following options are suggested. The dose of aspirin can be increased from once daily to twice daily or changed to an ADP receptor antagonist such as clopidogrel 75mg once daily or use combined aspirin and clopidogrel or start anticoagulation with VKA instead of antiplatelet treatment. We prefer the latter option more than the increasing the frequency of aspirin or changing to alternative antiplatelet treatment. Patients developing recurrence of VTE despite being on therapeutic anticoagulation with VKA may need to increase their target INR from 2.5 (2.0-3.0 to 3.5 (3.0 to 4.0) (Figure 2). Those who developed both arterial and venous thrombosis may need treatment with LDA and VKA, however the risk for bleeding is increased with this combination. Data on combined treatment with LDA and VKA in patients with MPNs with recurrent thrombosis are lacking.

If a patient develops recurrent event despite being on appropriate anticoagulation or antiplatelet treatment, careful attention should be paid to blood counts and cardiovascular risk factors and appropriate measures should be taken to optimize them. A multivariate analysis revealed that the significant predictors of subsequent arterial events were prior arterial events, hyperlipidemia, and hypertension[26]. Other significant associations with arterial thrombosis included advanced age (≥60 years), diabetes, hyperlipidemia, hypertension, and normal karyotype, and venous thrombosis was associated with younger age (≤ 60 years), female sex, history of major hemorrhage, and palpable splenomegaly[26].

In optimizing the blood counts, patients currently only on venesection or drugs that primarily target one cell line such as anagrelide which mainly control the platelet count, may need treatment with a broad-spectrum agent, such as hydroxycarbamide to bring down the hemoglobin and white cell count. Furthermore, there is evidence to suggest that anagrelide may increase the rates of arterial thrombosis[27]. Therefore, elderly patients or those at high risk for thrombosis who need tight control of all three cell lines should be managed with hydroxycarbamide or interferon rather than with anagrelide.

Patients with PV refractory or unable to tolerate hydroxycarbamide, may need treatment with JAK inhibitors such as ruxolitinib. However, the role of JAK2 inhibitors in similar group of patients with ET is not clear yet and this is under review. Evidence suggest that angiotensin converting enzyme (ACE) inhibitors could simultaneously control arterial blood pressure and abnormal erythropoiesis and consequently reduce the need of cytoreductive drugs in patients with PV[18;28]. Therefore, it seems more appropriate use ACE inhibitors in MPN patients with hypertension unless there is a contraindication.

After the first episode of VTE, the duration of secondary prophylaxis with VKA should be decided to balance the risk of hemorrhagic complications with that of recurrent VTE. In MPN patients, the overall rate of recurrent thrombosis after VTE is 6.0 to 6.5 per 100 patient-years compared reported rate of compared to 2.7 - 3.7 per 100 patient-years in patients without MPN [29;30]. Long-term treatment with VKA (INR 2.0–3.0) is associated with a clear benefit, reducing the incidence rate of recurrence from 48 to 69% with respect to off treatment[29]. A summary of the suggested anticoagulant management and duration of treatment in patients with VTE usual sites in MPN in provided in figure 2. Despite the increasing use of direct oral anticoagulants (DOACs) which include direct factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) and direct thrombin inhibitors (dabigatran) in place of VKA in many other conditions, in patients with MPN, there are not enough data to support the use of DOACs. The evidence on use of DOACs in MPN is limited to small number of patients (25 patients) where they appear to be safe and efficacious [31]. Therefore, use of these anticoagulants should be considered only in case by case basis by assessing the risk of bleeding vs thrombosis (Figure 2). Cerebral vein thrombosis occurs in about 1% of MPN patients, primarily in those with ET bearing the JAK2 V617F mutation [32]. Recurrence rates are higher, especially in spontaneous CVT related to MPN, and 30% of patients suffer recurrence despite anticoagulation and cytoreduction [32;33]. Patients with PV-related CVT should be treated with long-term anticoagulation with VKAs with target INR of 2.5 (2.0-3.0) and cytoreduction.

Those who develop recurrence of CVT despite being on therapeutic INR, need to have higher target INR, i.e. 3.5 (3.0-4.0).

Management of splanchnic or abdominal vein thrombosis

Thrombosis in the splanchnic veins including BCS is one of the main features of MPNs. The prevalence of SVT ranges from 1% to 23% in MPN, and is commonly seen in young women, probably due to exposure to additional risk factors such as contraceptive use[34;35]. Around 30% of patients with SVT are found to have MPN. This is even higher among patients with hepatic vein thrombosis or BCS in whom MPN is present in approximately 50%[9;36]. Patients with SVT carry high rates of morbidity and mortality and in addition to anticoagulation with LMWH followed by VKA, they may need additional interventions such as placement of stents in the abdominal veins; thrombolysis or liver transplant in some patients[9]. In the acute phase, the antithrombotic treatment of patients with SVT and MPNs does not differ from that of patients without MPNs [37]. They should be treated promptly with full-dose low molecular or unfractionated heparin followed by VKA, maintaining INR in the therapeutic range of 2.0–3.0. Notably, VKA monitoring can be difficult in patients with BCS and liver failure, due to the reduced production of coagulation factors altering the baseline INR. Recurrence of SVT is high and prevention is important because of significant morbidity and mortality associated with recurrence. Overall 25–30% of MPN-SVT patients suffer a recurrence of SVT by 10 years [38;39]. Although the optimal duration of VKA is unknown, in general life-long treatment is suggested, considering the presence of continuing risk factors for thrombosis. The role of DOACs has not been studied in MPN-related SVT and currently not recommended. Therefore, LMWH followed by VKA remains the standard of care. In addition to starting anticoagulation with LMWH promptly followed by VKA, patients with MPN related SVT may need antiplatelet treatment and control blood count with cytoreductive treatment. Patients with MPN and

SVT should have bone marrow assessment as cytopenia due to hepato-splenomegaly may mask the disorder. Patients with SVT and MPN need long term anticoagulation and control of the blood count. Even if the patient has normal blood cell counts and normal marrow, they require anticoagulation and monitoring of their blood cell count regularly. It is not clear whether cytoreduction or JAK inhibitor treatment is beneficial in this group. The effect of cytoreduction in MPN with SVT has not been studied systematically. Although cytoreduction was used in 40 – 70% patients across registries and did not uniformly influence recurrence risk, abnormally high blood counts due to inadequate cytoreduction were present in over half the patients with recurrent thrombosis[40]. This demonstrates the need for good control of cytoreduction. Venesection alone is not adequate to treat PV and cytoreduction should be undertaken in the presence of SVT. With cytoreduction, careful attention must be paid to avoid significant thrombocytopenia in the face of continuing anticoagulation and very often small doses of cytoreductive agents are sufficient to achieve therapeutic targets. It has been shown that treatment with ruxolitinib reduced the volume of the spleen size in a third of patients with MPN related SVT patients after 2 years [41]. Complications of treatment include bleeding, especially gastrointestinal and in particular, variceal haemorrhage[39;40]. Bleeding risk can be reduced by appropriate intervention to manage oesophageal varices and concurrent use of proton pump inhibitors.

The management of SVT in MPNs requires a multidisciplinary approach that may include a hematologist, a gastroenterologist, an interventional radiologist and a surgeon. In the case of clinical deterioration despite pharmacological therapy, patients with SVT should be considered for invasive procedures such as angioplasty with or without stenting, trans-jugular intrahepatic portosystemic shunt (TIPS), or surgical portosystemic shunt or liver transplantation [42].

Prevention of thrombosis during pregnancy and post-partum period

Pregnancy itself increases risk of thrombosis due to physiological changes in the hemostatic pathways. Prior thrombosis or hemorrhage, previous pregnancy complications and extreme thrombocytosis are considered to be risk factors for fetal and maternal complications.[9;35] Women with MPN are at risk of obstetric complications, such as fetal loss throughout all trimesters, intra-uterine growth retardation, prematurity, maternal thromboembolism and hemorrhage[9;10]. Skeith et al performed a meta-analysis to evaluate the risk of VTE in pregnant women with ET using 21 studies involving 756 pregnancies[43]. The absolute risk of VTE increased to 1% to 3% during the antepartum period and greater than 3% in the post-partum period. Therefore, the authors concluded that LMWH prophylaxis is suggested in the postpartum period and the routine thromboprophylaxis is not required during pregnancy, unless additional risk factors are present[43]. Furthermore, they suggested that the role of thromboprophylaxis requires a shared decision-making process, taking into account patient values and preferences, the risk of bleeding, and the risks and benefits of LMWH[43].

In addition to previous pregnancy loss and previous history of VTE or hemorrhage, factors that increase the risk of thrombosis in women even without MPN need to be taken in to consideration when deciding the thromboprophylaxis during pregnancy. Current guidelines suggest that all pregnant women with MPN (especially PV and ET) should receive LDA throughout the pregnancy[10]. However, aspirin should be given with caution during the third trimester due to possible effects on the ductus arteriosus and the risk of intracerebral hemorrhage in premature infants. The balance of benefits and risks of taking aspirin in pregnancy should be discussed with the patient. Women with MPN and standard risk, 6 weeks post-partum thromboprophylaxis with LMWH is recommended [10]. In women with JAK2 positive MPN, unless, there is a concern for increased risk of bleeding, we would consider prophylactic LMWH throughout pregnancy and 6 weeks post-partum. Woman with MPN in pregnancy should be managed by a multidisciplinary team and should be followed in a joint obstetric and hematology clinic.

Conclusion

Major causes of morbidity and mortality in patients with MPN are represented by arterial and venous thrombosis in addition to progression to myelofibrosis, and transformation to acute leukemia which is beyond the area of discussion in this review. Although, duration of anticoagulation following first episode of VTE in MPN has not been studied the overall rate of recurrent thrombosis after VTE is 6.0 to 6.5 per 100 patient-years. Antithrombotic therapy with VKA is associated with a clear benefit, reducing the incidence rate of recurrence by 48-69% compared to off treatment. Life-long oral anticoagulation with VKAs is the cornerstone of the antithrombotic treatment for SVT. DOACs can represent an alternative and preliminary data encourage comparative studies. The management of SVT in MPNs requires a multidisciplinary approach. Unless these contraindications are present, pregnant women with MPNs should receive aspirin throughout the pregnancy and should be followed in joint obstetric and haematology clinic. High risk women should receive prophylactic dose LMWH during pregnancy and 6 weeks post-partum. For women with MPN and standard risk, 6 weeks post-partum thromboprophylaxis with LMWH is recommended.

Authorship

DRJ Arachchillage performed the literature search and wrote the first draft. M Laffan and DRJ Arachchillage reviewed and approved the final manuscript

Disclosure of Conflicts of Interest

Authors have no conflicts of interest to declare

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Legends to figures

Figure 1. Mechanisms which, in myeloproliferative neoplasms (MPN), can increase the thrombotic risk through cell activation and inflammation.

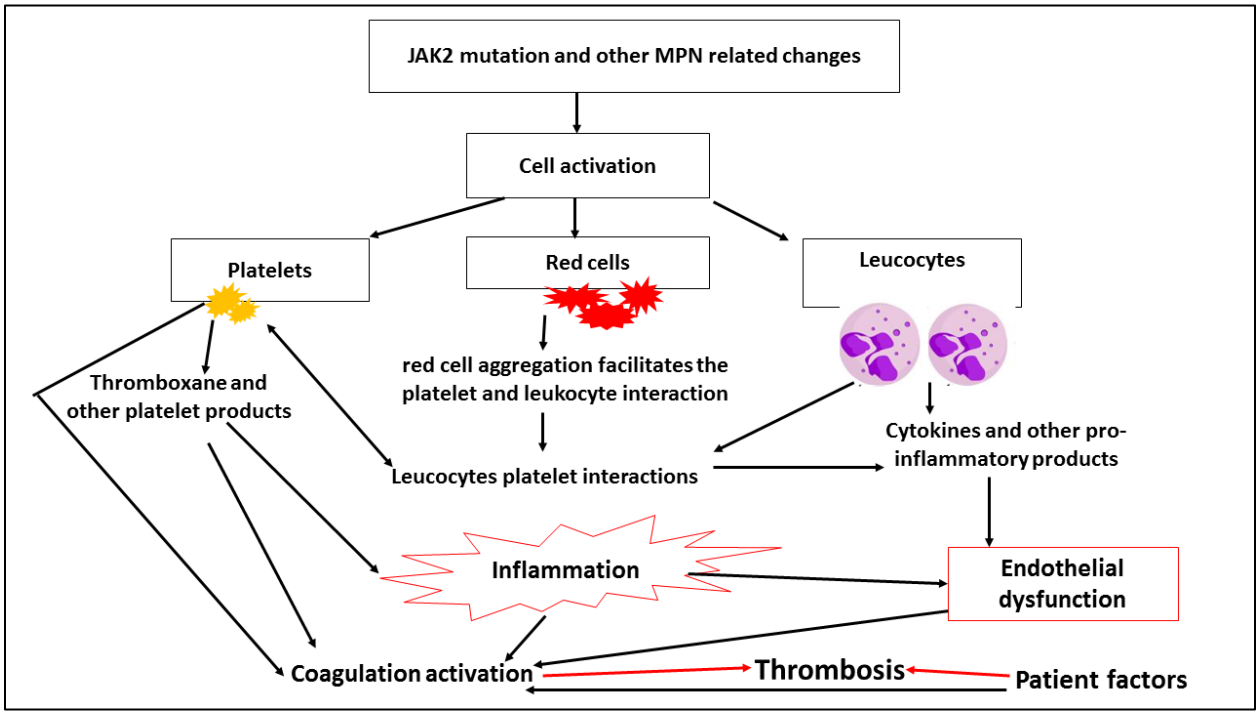
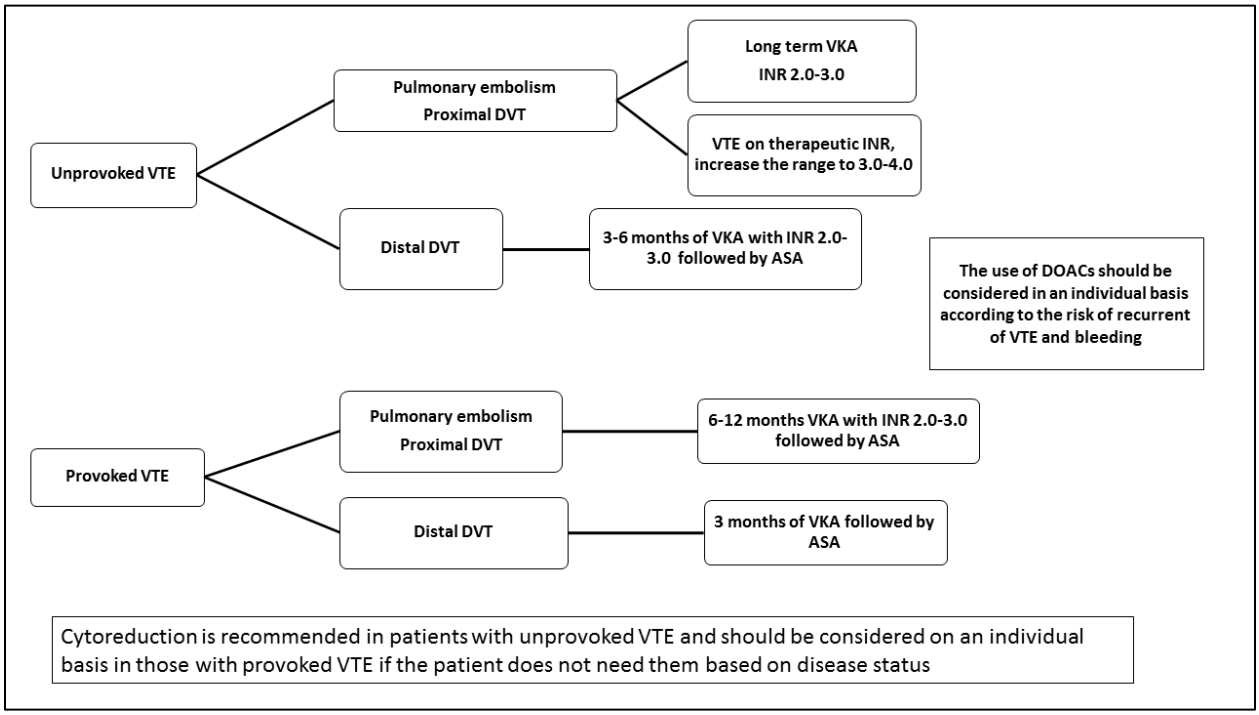


Figure 2. Management of venous thromboembolism at usual sites in myeloproliferative neoplasms



(VTE=venous thromboembolism, DVT= deep vein thrombosis, PE= pulmonary embolism, ASA= aspirin, DOACs= direct acting oral anticoagulant)