REVIEW

Complications and management of coagulation disorders in leukemia patients

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Abstract: Patients with leukemia are predisposed to various coagulation abnormalities. Thrombosis and bleeding continue to be a major cause of morbidity and mortality in leukemias. The pathophysiology of these disorders is unique, and not only the disease but also the treatment and other factors play a role. There has been an increase in the understanding of these disorders in leukemias. However, it is still difficult to predict when and which patients will have these complications. The evidence for the management of coagulation abnormalities in leukemias is still evolving and not as established as in solid malignancies. The management of these disorders is complex, and making clinical decisions is often challenging. In the era of specialization, where there are different hematologists looking after benign- and malignant-hematology patients, opinions of thrombosis experts are often sought by leukemia specialists. This review aims to bridge the gap in the knowledge of these disorders between these specialists.

Keywords: leukemia, coagulation, thrombosis, bleeding

Introduction

Coagulation disorders are common in leukemia patients. The incidence of thromboembolism (TE) in hematologic malignancies (including lymphoma and myeloma) stands at 4% per year. This is the fourth most common cause after pancreatic (11%), brain (8%), and lung cancers (4.4%).[1] The incidence of bleeding is the highest of all malignancies by virtue of the disease-related thrombocytopenia itself. Coagulation disorders seen in lymphoma, myeloma, and other solid malignancies are beyond the scope of this review. The reader may refer to excellent reviews and guidelines on these topics.[2,3] For the purpose of simplicity, we deal with each leukemia type with a case vignette, followed by epidemiology, pathophysiology, and management issues. All patients provided written informed consent for their case details to be published.

Coagulation disorders in acute lymphoblastic leukemia

Case vignette

GK, a 39-year-old woman diagnosed with pre-B-cell acute lymphoblastic leukemia (ALL), standard risk was started on the Berlin–Frankfurt–Münster (BFM)-90 protocol. Her blood counts at presentation were hemoglobin 45 g/L, platelets 18×10⁹/L, and white-cell count 1.2×10⁹/L. She received native *Escherichia coli* L-asparaginase as part of the induction therapy. In the fourth week after completion of the L-asparaginase course, she presented with generalized tonic–clonic seizures and right-sided hemiparesis.

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Computed tomography suggested bifrontal hemorrhage. Magnetic resonance venography of brain confirmed superior sagittal sinus thrombosis. Her blood counts were hemoglobin 80 g/L, platelets 85×10^9/L, and white-cell count 2.8×10^9/L. Her fibrinogen levels were normal throughout the course of L-asparaginase. She was started on a therapeutic dose of low-molecular-weight heparin (LMWH). LMWH was dose-modified for thrombocytopenia during the intensive phase. She was not rechallenged with L-asparaginase during the reinduction phase. She remains in complete remission, with minimal residual disease negative at end of induction. LMWH was continued for 6 months. Her focal neurological deficit recovered, and she had no recurrence of thrombosis.

Epidemiology

The reported incidence of TE in childhood ALL varies from 1.1% to 36.7%.[4] This wide variation is due to differences in TE diagnosis and treatment protocols. This incidence is even higher in adolescent and young adult (34%) and adult patients (43%) on L-asparaginase.[5] The commonest sites for TE are central nervous system (CNS; 50%) and deep vein thrombosis (43%). The overall mortality of TE in ALL varies from 0 to 4.8%.[4] On the contrary, deaths due to bleeding in ALL are less common than in acute myeloid leukemia (AML).[6]

Pathophysiology

The clinical presentation of TE or bleeding is an outcome of the delicate balance between procoagulant and anticoagulant forces at play in a patient (Figure 1). There are several studies showing increased thrombin generation shown by thrombin–antithrombin (AT) complexes at diagnosis and in initial therapy for ALL. Factor VIII, von Willebrand factor (vWF), and fibrinogen are positive acute phase reactants.[7] Besides this, ALL cells also express cancer procoagulant (CP).[8] CP activates factor X directly, independently of factor VII.[9] Disseminated intravascular coagulation (DIC) is underrecognized in ALL, with prevalence of around 14% at diagnosis and doubling to 27% during induction therapy.[10]

Chemotherapy in ALL augments the thrombogenic potential. Of these, L-asparaginase, which depletes the ALL cells of the essential amino acid asparagine, also ends up depleting the procoagulant (fibrinogen, factors V, VII, VIII, IX, X, and XI) and anticoagulant (AT, plasminogen, protein C/S) proteins. L-Asparaginase may in fact cause a prothrombotic state, as it reverses the procoagulant proteins earlier than anticoagulant proteins.[11] *E. coli* asparaginase, which is more potent than *Erwinia* asparaginase, has more effect on the coagulation parameters.[12] Steroids add to the prothrombotic state by increasing plasma levels of
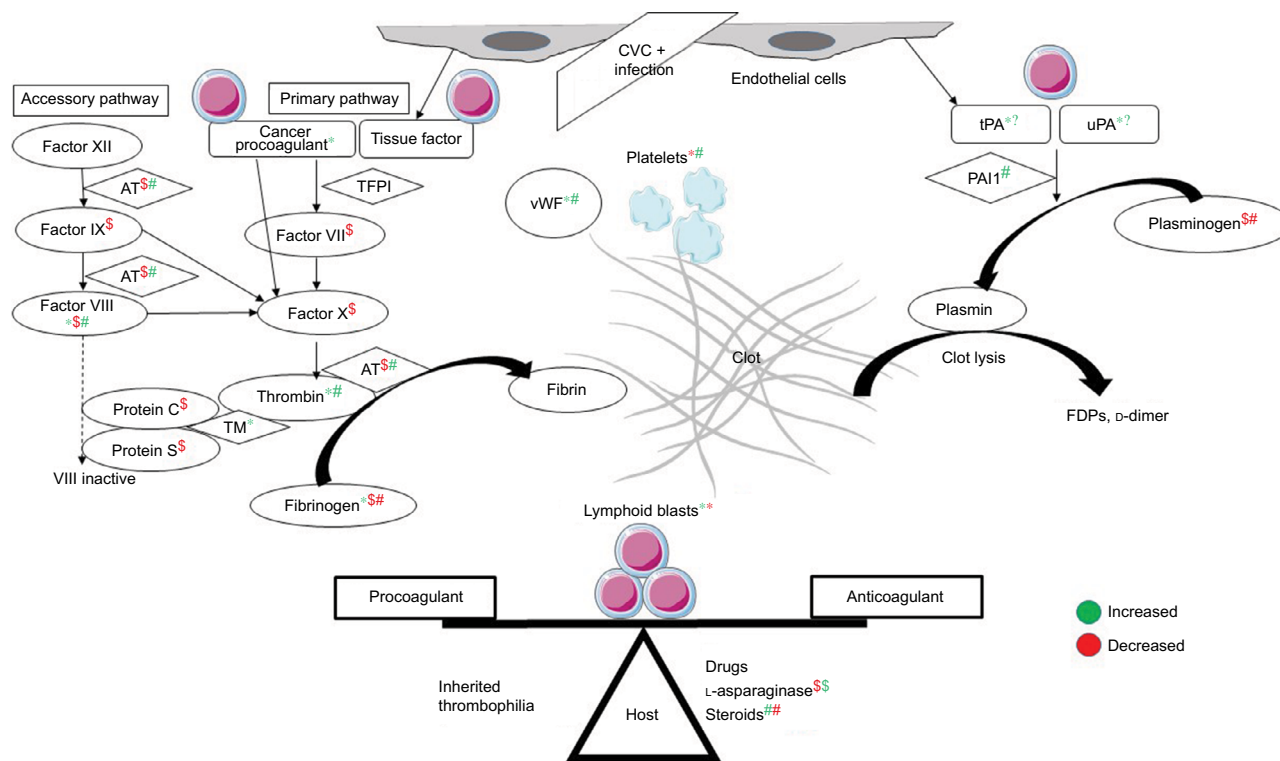

Figure 1 Balance between procoagulant and anticoagulant forces in ALL and interactions among host, disease, and treatment related factors.
Notes: *Effect of lymphoid blasts; $effect of L-asparaginase; #effect of steroids, on coagulation parameters; green color is increased effect and red color is decreased effect.
Abbreviations: ALL, acute lymphoblastic leukemia; CVC, central venous catheter; TFPI, tissue-factor pathway inhibitor; vWF, von Willebrand factor; AT, antithrombin; TM, thrombomodulin; FDPs, fibrin-degradation products.

prothrombin, factor VIII/vWF, and PAI1 and decreasing plasminogen and fibrinogen.[13] Dexamethasone may be associated with less risk of TE than prednisone.[14] Central venous lines are the other reason for TE, with incidence as high as 30%, depending on the technique and site of insertion.[15] A variable 18%–40% of cases may have inherited thrombophilia.[16] Use of granulocyte/granulocyte-monocyte colony-stimulating factors during episodes of neutropenia is also associated with thrombosis at an incidence of 1.2% and 4.2%, respectively. This is through increased tissue-factor (TF) and factor-VIII levels.[17] T-cell ALL patients are at higher risk of both TE and hemorrhagic complications, due to hyperleukocytosis.[18] Thrombocytopenia – at diagnosis or therapy-related – is one of the major factors contributing to bleeding in ALL. Infections can tilt the balance either way of systemic inflammatory response syndrome or consumptive coagulopathy.

Investigations

Recommended tests include activated partial thromboplastin time (aPTT), international normalized ratio (INR), and fibrinogen levels (AT optional) prior to, during native asparaginase dosing, and 1 week after polyethylene glycol–asparaginase therapy. For prevention of TE, research using AT prophylaxis have shown reduced incidence of TE, but this was not powered for efficacy, and hence the role of AT replacement remains inconclusive.[19] Though prophylactic fresh frozen plasma/cryoprecipitate to replace AT is associated with no CNS TE events, neither it nor LMWH lower the incidence of TE on L-asparaginase.[20,21] Some centers use both anticoagulation and AT replacement for AT levels <60%.[22] At our center, we give cryoprecipitate for fibrinogen <100 mg/dL.

Treatment

Development of TE while on L-asparaginase used to lead to discontinuation of asparaginase in up to 75% patients, which led to inferior event-free survival outcomes.[23,24] However, with current strategies of rechallenging asparaginase and continued anticoagulation, outcomes have been similar.[5] Current expert recommendations are to discontinue asparaginase only for CTCAE (Common Terminology Criteria for Adverse Events) grade 4 CNS thrombosis or bleed. For all grade 3 events and grade 4 non-CNS events, asparaginase needs to be withheld till resolution of clinical signs and either anticoagulation or coagulant therapy is stable. Asparaginase may be resumed at lower doses and/or longer intervals. Asparaginase need not be withheld for asymptomatic lab abnormalities.[25] As regards prophylactic platelet transfusions, the restrictive strategy with the standard trigger set at $10 \times 10^9/L$ has remained unchanged over the past decade.[26]

There have been no prospective randomized control trials on anticoagulant choice, dose, and duration in patients with leukemia. Most recommendations have been derived from extrapolation from studies done in patients with solid-organ malignancies. These guidelines endorse the use of LMWH as first-line therapy during the first 3–6 months after the diagnosis of malignancy-associated venous TE (VTE) based on the 2003 CLOT study.[27–30] There have been recent expert recommendations on managing thrombosis in the setting of leukemia with thrombocytopenia.[31–33] The consensus for anticoagulation dose modification in the setting of thrombocytopenia is as given in Tables 1 and 2. For catheter-related VTE, recommendations are to keep the catheter and continue anticoagulation till the catheter is in place or at least 3 months, whichever is longer. Catheter removal is only required if the device is dysfunctional, infected, or

Table 1 Acute thrombosis (0–30 days after diagnosis of VTE)

Platelet count ($10^9/L$) (posttransfusion)	Platelet transfusion[a]	Anticoagulant dosage
Platelets ≥50	No	Dalteparin 200 U/kg SC once daily/full-dose LMWH
Platelets 20–50	Yes	Dalteparin 100 U/kg SC once daily/half-dose LMWH
Platelets <20	Yes	Hold anticoagulation

Note: [a]Transfusion to platelet count ≥$20 \times 10^9/L$ to allow at least 50% anticoagulant dose.
Abbreviations: VTE, venous thromboembolism; LMWH, low-molecular-weight heparin.

Table 2 Chronic thrombosis (>30 days after diagnosis of VTE)

Platelet count ($10^9/L$)	Platelet transfusion[a]	Anticoagulant dosage
Platelets ≥50	No	Dalteparin 150 U/kg SC once daily/full-dose LMWH
Platelets 20–50	No	Dalteparin 75 U/kg SC once daily/half-dose LMWH
Platelets <20	No	No anticoagulation: do not insert filter

Note: [a]Platelet transfusion not indicated for anticoagulant dose.
Abbreviations: VTE, venous thromboembolism; SC, subcutaneously; LMWH, low-molecular-weight heparin.

not required. For non-catheter-related TE, anticoagulation is recommended for at least 6 months and indefinitely for active malignancy or persistence of risk factors for recurrence.[3] The decision to stop anticoagulation beyond 6 months in patients under treatment of a malignancy that is in complete remission is unclear. This is on a case-by-case basis after taking the risk:benefit ratio into consideration. To summarize, in this case, the patient had a grade 4 CNS vascular event on L-asparaginase, despite normal fibrinogen levels. She was managed with dose-modified anticoagulation as mentioned, and not re-challenged with L-asparaginase.

Coagulation disorders in acute myeloid leukemia
Case vignette

RM, a 28-year-old lady, presented with a 4-day history of gangrenous changes in both hands (left > right) and feet. On clinical examination, she had absent ulnar, dorsalis pedis, and posterior tibial artery pulse bilaterally. Her investigations revealed hemoglobin 63 g/L, platelets 39×10^9/L, and white cell count 33.2×10^9/L with 85% blasts + promyelocytes. Her coagulogram showed PT 20 seconds, control 14 seconds, INR 1.4, aPTT 31 seconds, control 25–32 seconds, and elevated D-dimer and fibrin-degradation products. Her fibrinogen levels were normal, however. She was started on treatment with all-*trans* retinoic acid (ATRA) and arsenic on suspicion of acute promyelocytic leukemia (APML) and DIC. This is the first line at our center, even in high-risk APML.[34] She was given prophylactic steroids plus hydroxyurea to prevent differentiation syndrome. Computed tomography angiography confirmed the presence of arterial thrombosis in the distal ulnar and posterior tibial arteries. This is a rare presentation of APML, but included here to emphasize the management issues in this case. Given her state of established gangrene with line of demarcation and DIC, she could not be started on any vascular intervention or anticoagulation/antiplatelets. ATRA + arsenic and platelet support was continued. She attained complete remission at the end of 4 weeks. She underwent bilateral below-knee amputation with left phalangeal disarticulation for her dry gangrene 6 months later. She continues to be in remission 4 years later. This outcome is similar to what has been described in case reports.[35]

Epidemiology

Most cases of AML-M3/APML have DIC at diagnosis. The incidence of DIC in AML-non-M3 is 10%–50%, depending upon the subtype of leukemia and diagnostic criteria for DIC.[36,37] The incidence of thrombosis in AML-non-M3 and APML at diagnosis is 3.2% and 9.6%, respectively. The same at follow-up is 1.7%–8.5% and 8.4%–11% respectively.[38,39] In APML, most cases occur before or during induction therapy with ATRA. Arterial events are commoner than venous events. Thrombosis and severe hemorrhage co-occur in 15% of cases.[40] The incidence of isolated severe bleeding remains high in APML – around 21%. The case-fatality rate of these episodes can be as high as 50%. The incidence of early-death rates in APML has remained unchanged over the years: at 5%–10%, even in the ATRA era.[41] The incidence of thrombosis in APML at our center is 7.4% (n=136), with equal numbers of arterial and venous TE. The incidence of severe bleeds is 28%, with the early-death rate due to bleeding being 7.4% (Varma et al, unpublished data). Predictors of thrombosis include elevated white-cell count, Bcr3 isoform, FLT3 internal tandem duplication, and expression of CD2 and CD15 on promyelocytes.[42] Though not a coagulation defect in principle, hyperleukocytosis can be seen in AML when the white-cell count is $>100\times10^9$/L. This leads to leukostasis and vascular occlusion in any vital organ.[43]

Pathophysiology

The DIC seen in APML is a double-edged sword for thrombosis and bleeding (Figure 2). Procoagulant forces are CP expressed on leukemic promyelocytes.[44] TF from endothelial cells is exposed by cytokines (IL1 and TNFα) released from apoptotic leukemic cells.[45–47] TF is the site of activation of factor VII. TF-expressing microparticles in APML have procoagulant activity.[48] Anticoagulant forces are elevated uPA and tPA and low PAI1.[49,50] Leukemic promyelocytes express annexin II, which accelerates the conversion of plasminogen to plasmin and thus causes primary fibrinolysis.[51] Cerebral endothelial cells also express this annexin II, which explains the high incidence of intracerebral bleeds seen in APML.[52] Emerging evidence points to podoplanin expression on leukemic promyelocytes causing platelet aggregation as a novel mechanism for bleeding.[53] The role of proteases like elastase and chymotrypsin released from leukemic promyelocytes on fibrinolysis, if any, is minor.[54] ATRA can reverse these changes through various mechanisms of reduced expression of TF, CP, and annexin II and counteracting the effect of cytokines.[55] ATRA may in fact tilt the balance to a prothrombotic state, as it reverses the procoagulant proteins earlier than anticoagulant proteins, similar to L-asparaginase.[56] A novel cell-death pathway termed "ETosis" has been described recently in APML blasts treated with ATRA. This process releases intact chromatin in the extracellular space. This
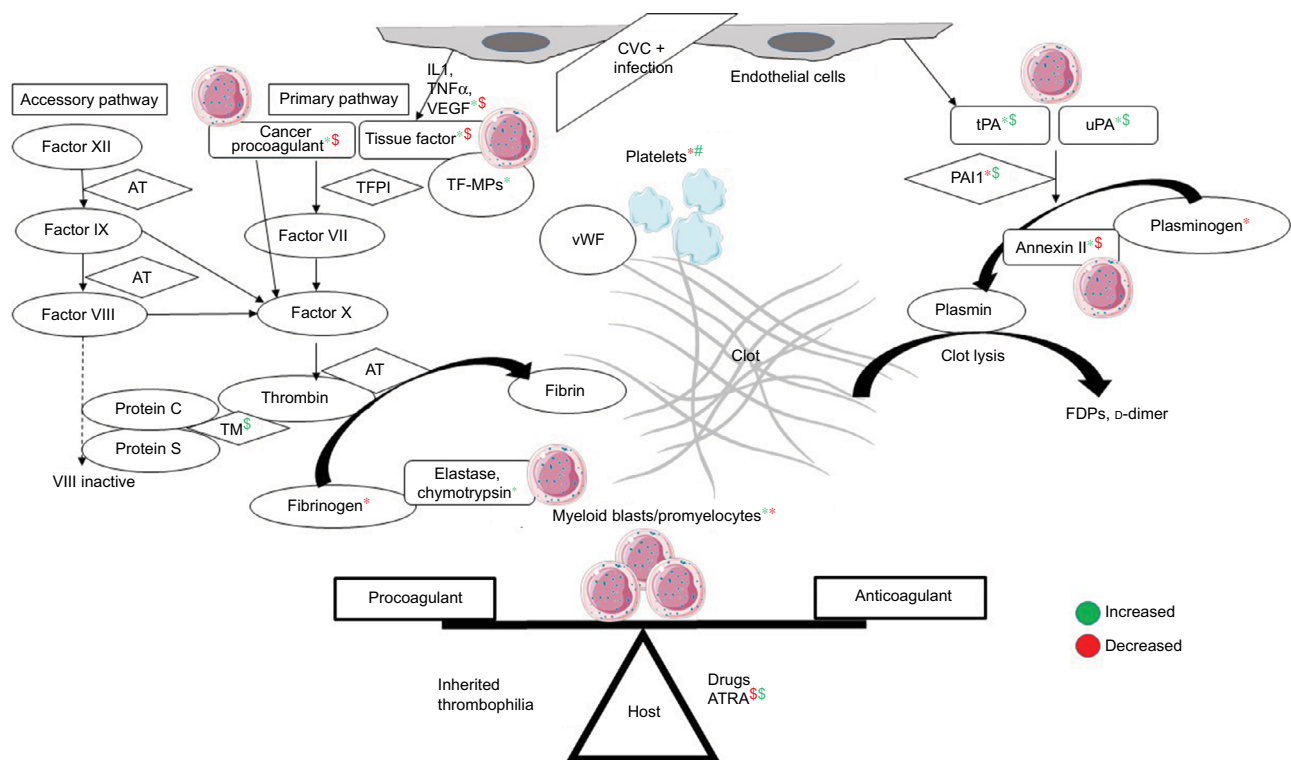
Figure 2 Pathophysiology of disseminated intravascular coagulation in APML and the role of ATRA in counteracting it.
Notes: *Effect of myeloid blasts/promyelocytes; ‡effect of ATRA on coagulation parameters; green color is increased effect and red color is decreased effect.
Abbreviations: APML, acute promyelocytic leukemia; ATRA, all-*trans* retinoic acid; CVC, central venous catheter; TFPI, tissue-factor pathway inhibitor; TF-MPs; TF-expressing microparticles; vWF, von Willebrand factor; AT, antithrombin; TM, thrombomodulin; FDPs, fibrin-degradation products.

extracellular chromatin has multifold effects of increasing thrombin and plasmin generation and causes fibrinolysis resistance and endothelial activation.[57]

Investigations

Routine coagulation tests may reveal overt DIC with prolongation of PT, variable aPTT, low fibrinogen levels and platelet counts, and elevated D-dimer and fibrin-degradation products.[58] However, these variables do not correlate well with the severity of bleeding or thrombosis.[41] No single test can confirm or rule out DIC. The International Society on Thrombosis and Haemostasis overt DIC score may miss subclinical DIC in acute leukemia.[10] A recent study showed that a high D-dimer level >4 mg/L was most predictive for thrombosis in AML-non-M3 patients.[59] Other tests of activated clotting like prothrombin fragment 1+2, thrombin–AT complex, and fibrinopeptide A may be helpful, but are not routinely available. Elevated white-cell count (>20×109/L) is an independent predictor of early hemorrhagic death in APL.[60]

Treatment

Both ATRA and arsenic trioxide (ATO) can reverse the coagulopathy of APML within 4–11 days. This underscores the importance of starting ATRA in the emergency department

whenever a diagnosis of APML is suspected. The incidence of thrombosis in the ATRA era is higher than in the pre-ATRA era.[40] However, the incidence of TE in ATRA + ATO is lower than in ATRA + chemotherapy in non-high-risk APML patients.[61] European Leukemia Net guidelines recommend fresh frozen plasma, fibrinogen, and/or cryoprecipitate to maintain the fibrinogen concentration above 100–150 mg/dL. In APML, the platelet-transfusion threshold is more liberal, and the aim is to maintain a count >30–50×109/L. The role of heparin, tranexamic acid, or other anticoagulant or antifibrinolytic therapy is unclear and not recommended as part of routine practice.[62] On the contrary, combining ATRA with tranexamic acid may lead to fatal thromboembolism.[63] There is insufficient evidence to recommend thrombopoietin mimetics, recombinant factor VIIa, antifibrinolytics, desmopressin, activated protein C, or recombinant human soluble thrombomodulin to prevent or treat bleeding in hematological malignancies.[64–66] The role of leukapheresis in hyperleukocytosis to prevent early mortality is also unclear; in fact, it may lower platelet counts and fibrinogen and prolong prothrombin time.[67,68] Early cytoreductive chemotherapy and supportive care with platelets, fresh frozen plasma, cryoprecipitate, or fibrinogen concentrates are the only recommended measures to prevent or treat bleeding associated with DIC in AML.[69]

In summary, the patient had APML with DIC manifesting as acute arterial thrombosis of the extremities. She was managed with ATRA + ATO and supportive transfusions without anticoagulation. She survived the leukemia, but lost her limbs to gangrene.

Coagulation disorders in myeloproliferative neoplasms
Case vignette

MS, a 19-year-old man, presented with a 1-month history of abdominal pain. He had a massive splenomegaly with thrombosis of the splenoportal axis. His blood counts at presentation were hemoglobin 108 g/L, platelets 668×10^9/L, and white cells 5.6×10^9/L, with a normal differential count. His bone marrow suggested a diagnosis of essential thrombocytosis (ET). His $JAK2^{V617F}$-mutation status was positive. The final diagnosis was high-risk ET with splanchnic vessel thrombosis. On upper gastrointestinal endoscopy, he had no esophageal varices, but had multiple small gastric varices at diagnosis. He was given LMWH and bridged to warfarin titrated to an INR of 2–3. Aspirin was withheld, due to gastric varices. He was also started on hydroxyurea 500 mg orally twice a day titrated to a normal platelet count. He had an episode of hematemesis a year later, requiring interruption of warfarin and glue injection of the gastric varices. Given the risk of gastric variceal bleeding with aspirin, and considering the risk:benefit ratio of anticoagulation, he was restarted on warfarin. The plan is to continue indefinite anticoagulation, with periodic upper gastrointestinal endoscopy for varices.

Epidemiology

Of the chronic myeloproliferative neoplasms (MPNs), polycythemia vera (PV), ET, and primary myelofibrosis (PMF) are most associated with thrombosis and bleeding. The prevalence of TE at the time of diagnosis in PV, ET, PMF is 4%–11%, 2%–8%, and 3%–7%, respectively. The incidence of TE thereafter is 2%, 0.6%, and 0.6% per year, respectively.[70] Arterial thrombosis (70%) is more common than venous TE (30%). MPNs are also the etiology in abdominal splanchnic vessel thrombosis (extra- + intrahepatic veins leading to Budd–Chiari syndrome [BCS], portal vein thrombosis, and mesenteric vein thrombosis). The prevalence of latent or manifest MPNs is 40% in BCS and 30% in portal vein thrombosis. $JAK2^{V617F}$ mutation without manifest MPNs is seen in 17.1% of BCS and 15.4% of portal vein thrombosis.[71] In chronic myeloid leukemia (CML), tyrosine-kinase inhibitors increase the risk of arterial (4.78%) and venous (0.72%) TE. The risk is higher with newer tyrosine-kinase

inhibitors (0.96%) than imatinib (0.27%).[72] In contrast to thrombosis, serious bleeding occurs in 5.5% of MPN patients.[73] The incidence of dasatinib-induced platelet dysfunction leading to serious bleeding in CML patients is 7%.[74] The incidence of thrombosis in PV at our center is 25%, with equal numbers of arterial and venous events.[75] The incidence of thrombosis and bleeding in ET at our center is 33.3% and 8.3%, respectively. A quarter of thrombotic events are arterial (Varma et al, unpublished data).

Pathophysiology

The mechanism of thrombosis in MPNs is multifactorial (Figure 3). Besides thrombocytosis, platelets aggregate due to upregulation of p-selectin, thrombospondin and GPIIB/IIIA receptors.[76] Besides leukocytosis, activated leukocytes form aggregates with platelets.[77,78] Erythrocytosis causes hyperviscosity; erythrocytes also show increased adherence to vascular endothelia.[79] Other mechanisms of thrombosis include microparticles and inflammation-mediated activation of endothelia.[80,81] Using novel gene-expression meta-analysis, certain coagulation-related genes have been identified to be associated with thrombosis in MPN. These include *IGF2R*, *PROS1*, *SELPLG*, and *ITGB2*.[82] The etiology of bleeding in MPN is multifactorial. Acquired von Willebrand syndrome is seen in patients with platelet counts $>10\times10^9$/L.[83] At these high counts, vWF binds to platelets and undergoes proteolysis with a resultant depletion of large multimers.[84] Besides this, there is evidence of platelet dysfunction in ET.[85] Other reasons for bleeding include treatment for disease and TE, thrombocytopenia due to disease progression, hypersplenism, liver dysfunction, and acquired hemophilia.[86]

Investigations

Acquired von Willebrand syndrome should be ruled out in all patients with platelet counts $>10\times10^9$/L before starting these patients on aspirin. Diagnosis of acquired von Willebrand syndrome involves showing a reduced function:antigen ratio (vWF:Act/Ag, vWF:Act or ristocetin-cofactor assay<30%) and loss of high-von Willebrand multimers.[87]

Treatment

Risk factors for recurrent thrombosis in PV and ET are age >60 years, history of thrombosis, *JAK2/MPL*-mutation status, *JAK2*-allele burden, and cardiovascular (tobacco use, hypertension or diabetes mellitus, leukocytosis $>11\times109$/L) in ET.[88] The goal of treatment in PV/ET is to prevent thrombohemorrhagic complications. Phlebotomy to achieve a hematocrit level <45% is standard treatment in all PV patients.[89] All
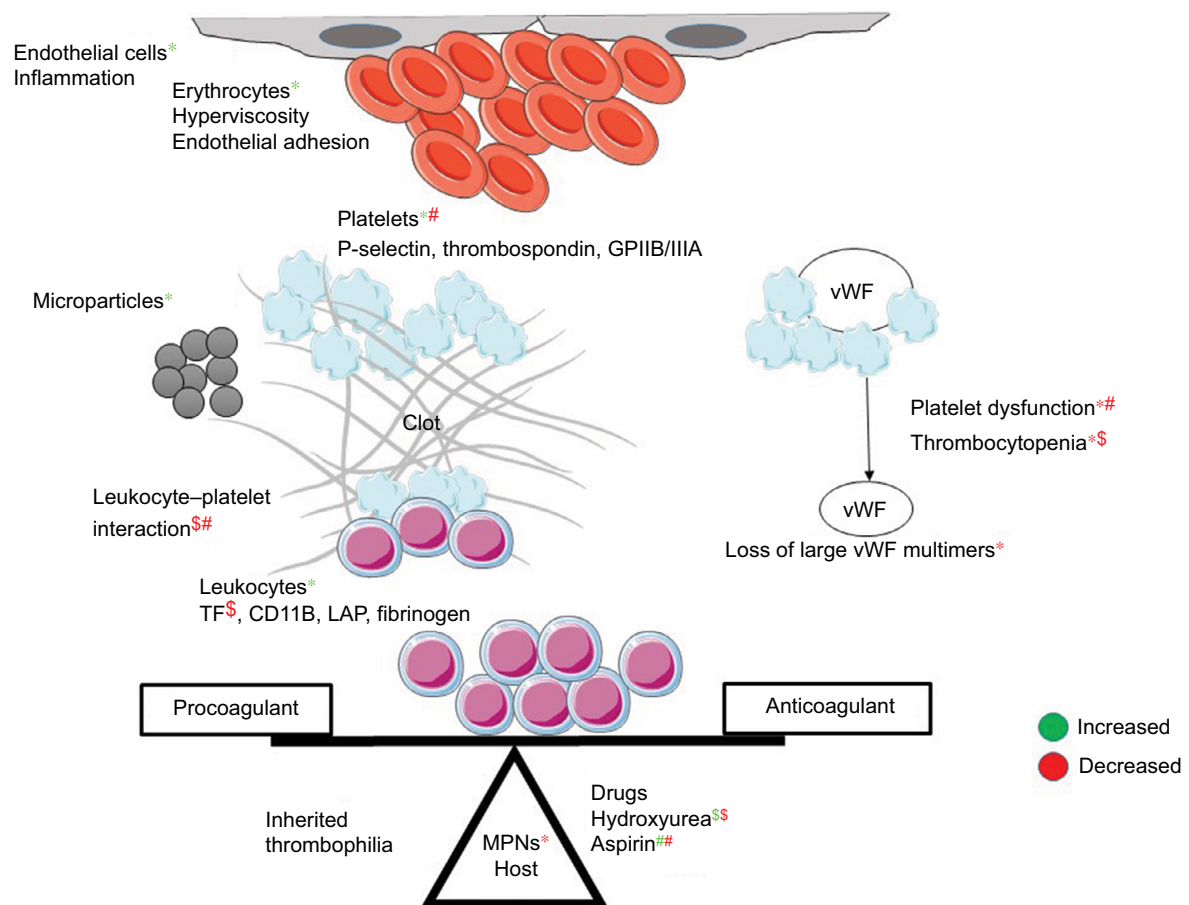
Figure 3 Pathophysiology of coagulation disorders in MPNs.
Notes: *Effect of MPN; $effect of hydroxyurea; #effect of aspirin on coagulation parameters; green color is increased effect and red color is decreased effect.
Abbreviations: MPNs, myeloproliferative neoplasms; vWF, von Willebrand factor.

low-risk PV and ET patients, except those with acquired von Willebrand syndrome, should get low-dose aspirin (40–100 mg/day). For high-risk PV or ET patients, hydroxyurea is recommended to target a platelet count in the normal range. All these measures reduce the risk of vascular events, including thrombosis and bleeding.[90] Anagrelide is falling out of favor, due to its increased risk of arterial thrombosis and major bleeding.[91] The requirement of phlebotomy on hydroxyurea correlates with the risk of thrombosis in PV patients.[92] Both aspirin and hydroxyurea reduce platelet–leukocyte complex formation and downregulation of leukocyte TF expression by hydroxyurea.[78,93] Ruxolitinib, a JAK2 inhibitor, is approved to treat MF and hydroxyurea-intolerant PV. It causes thrombocytopenia in 68% of patients and grade 3–4 thrombocytopenia in 13% of patients.[94] A meta-analysis has shown that ruxolitinib reduces the risk of both arterial and venous thrombosis in PV and PMF patients. This is believed to be due to inhibition of JAK-mediated inflammation by ruxolitinib.[95]

As regards treatment of VTE events, standard LMWH and vitamin K antagonists (VKAs) are used. The risk:benefit ratio of bleeding versus recurrent thrombosis needs to considered

on a case-by-case basis. The combination of LMWH/ VKAs and aspirin increases the risk of bleeding to 2.8% per patient-year.[73] The decision to stop anticoagulant therapy at 3–6 months is influenced by the preferences of an informed patient and risk of thrombosis. Recurrent VTE/cerebral or hepatic vein thrombosis, life-threatening VTE, and progressive MPNs uncontrolled with cytoreductive therapy would require indefinite treatment.[96] Because the risk of recurrent thrombosis is doubled on stopping anticoagulation and the risk of bleeding on VKA is the same as the non-MPN population, secondary prophylaxis should be continued for an indefinite period.[97] Aspirin should be continued in patients stopping anticoagulation. There are sparse data on the use of direct oral anticoagulants in hematological malignancies. These show no significant risk reduction in major bleeding compared to LMWH.[98] However, there are ongoing randomized trials addressing this issue.[99] If their use is considered, attention must be given to interactions with drugs used for treatment of the underlying disease (Table 3).[100] To summarize, the young patient had high-risk JAK2 + ET and splenoportal vein thrombosis. He was managed with hydroxyurea and VKAs.

Table 3 Drug interactions between DOACs and TKIs

TKI	Dabigatran	Rivaroxaban	Edoxaban	Apixaban
Imatinib	–	–	–	C
Nilotinib	–	–	–	C
Dasatinib	C	C	C	C
Ibrutinib	C	C	C	C

Note: Risk category C: monitor therapy for enhanced anticoagulant effect of anticoagulants.
Abbreviations: DOACs, direct oral anticoagulants; TKIs, tyrosine-kinase inhibitors.

He could not be given aspirin, due to the presence of gastric varices. He will need indefinite anticoagulation, given the risk of recurrent thrombosis in this population.

Coagulation disorders in chronic lymphocytic leukemia
Case vignette

HK, a 62-year-old lady, with known chronic lymphocytic leukemia (CLL) with 11q deletion and unmutated *IGHV* after early relapse on bendamustine–rituximab, was started on ibrutinib 420 mg daily for bulky lymphadenopathy in April 2016. Her complete blood counts at baseline were hemoglobin 100 g/L, platelets 79×10^9/L, and absolute lymphocyte count 231×10^9/L. Her baseline coagulogram was normal (PT 15 seconds, INR 1.2, aPTT 32 seconds, control 32 seconds). Within 2 weeks, her absolute lymphocyte count had risen to 412×10^9/L and platelets had dropped to 44×10^9/L. She had gum bleeding with a spontaneous hematoma of 10×15 cm in her left gluteal region. HK had grade 1 thrombocytopenia at baseline. She developed grade 3 thrombocytopenia with major but non-life-threatening bleeding. Her repeat coagulogram was normal (PT 14 seconds, control 14 seconds, INR 1, aPTT 31 seconds, control 32 seconds). This drop in platelet counts was due to ibrutinib, and was held till the resolution of hematoma and platelet count >50×10^9/L. Ibrutinib was restarted at the same dose. There was no recurrence of bleeding. At 1-year follow-up, her platelet count is up to 100×10^9/L.

Epidemiology

The incidence of at least one episode of severe bleeding in CLL is reported to be as high as 18%.[101] This is often seen with autoimmune or disease-related thrombocytopenia. Acquired hemophilia with inhibitors to factor VIII are rare causes of bleeding.[102] Bleeding assumes much more importance in the era of ibrutinib. While early studies showed major bleeding episodes occurred in 9% and 4% of CLL patients on anticoagulants and antiplatelets, later studies have this incidence at 2% and 1%, respectively.[103,104] CLL has not been associated with a high incidence of thrombosis. However,

recent studies have shown incidence rates may be as high as other leukemias – 5%–11%.[105,106] The risk factors for VTE is these studies were age >60 years, advanced stage of CLL, CLL treatment, and inherited thrombophilia.

Pathophysiology

At baseline, CLL patients have impaired platelet function assessed by platelet-function assay using epinephrine and adenosine diphosphate. Collagen-induced platelet aggregation is further impaired on initiating ibrutinib. Though factor VIII and vWF levels are elevated at baseline in most patients, their levels decline with ibrutinib. Low levels of factor VIII, vWF, and epinephrine-closure time on platelet-function assay predict bleeding in patients taking ibrutinib. There is no difference in platelet counts in patients who do and do not bleed. Bleeding risk decreases over time.[107]

Investigations

Recommended tests include PT, aPTT, INR, and platelet counts at baseline. Bone-marrow examination should be done at baseline in thrombocytopenic patients to confirm or rule out a diagnosis of autoimmune thrombocytopenia. PT, aPTT, INR, and platelet counts should be repeated whenever there is clinical bleeding. Platelet counts should be repeated before each monthly cycle.

Treatment

Patients need to be told to report any bleeding episodes and hold ibrutinib for any medical or dental procedures. Ibrutinib needs to be held for at least 3–7 days pre- and postsurgery, depending upon the surgery and risk of bleeding.[108] While there are no guidelines to hold ibrutinib if thrombocytopenia is due to disease, ibrutinib may be held for drug-related grade 4 thrombocytopenia (<25×10^9/L) or grade 3 thrombocytopenia (<50×10^9/L) with bleeding. It is restarted when platelet count rises to ≥50×10^9/L.[109] Treatment of idiopathic thrombocytopenic purpura, disease-related thrombocytopenia, and acquired hemophilia involves steroids or immunosuppression to treat underlying CLL. Anticoagulation is required in

5%–10% of patients on ibrutinib who develop atrial fibrillation.[110] Using direct oral anticoagulants in this setting needs interactions with ibrutinib to be taken in to consideration (Table 3).[111] Patients on concurrent anticoagulants or antiplatelets should be watched for bleeding.[112] The CLL patient mentioned in the vignette had grade 4 thrombocytopenia with non-life-threatening bleeding on ibrutinib. This mandated holding ibrutinib till platelet recovery. Subsequently, her platelet counts rose to $>100\times10^9$/L, as has been suggested to happen in 68% of patients on ibrutinib by 6 months.[107]

Conclusion

In summary, coagulation disorders are common in leukemia. Thrombosis is as common as in solid malignancies. It is difficult to predict which patients will have bleeding and/or thrombosis. We need better predictors and coagulation tests to identify such patients. More research with prospective randomized control studies is needed on the role of novel oral anticoagulants, anticoagulant choice, dosing, and duration in hematologic malignancies.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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