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EXPERT REVIEWS

Thromboembolic and bleeding complications in acute leukemia

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The risk of both thromboembolic and bleeding complications is high in acute leukemia. This double hazard has a significant negative impact on the morbidity and mortality of patients with this disease. The clinical manifestations of both complications show special features specific to the form of acute leukemia. Recognition of these characteristics is important in the diagnosis and management of acute leukemia. In this article, several additional issues are addressed, including the features of bleeding and thrombosis in acute promyelocytic leukemia, the current understanding of the leukostasis syndrome and the iatrogenic complications including catheter-associated thrombosis, and the adverse effects of therapeutic agents used in acute leukemia. As regards the bleeding complications, thrombocytopenia is a major cause. Corrective measures, including recent guidelines on platelet transfusions, are provided.

KEYWORDS: acute leukemia • acute promyelocytic leukemia • anticoagulation • fibrinolysis • hemorrhage • leukostasis • platelet transfusion • thrombosis

In 1865, Armand Trousseau observed 'phlegmasia alba dolens' in two patients with gastric cancer and preached that unexpected migratory thrombophlebitis could be a forewarning of an underlying malignant process [1]. Since then, the association between cancer and thrombosis has been well established [2]. Hematological malignancies carry a significant risk of venous thromboembolism (VTE), as do solid tumors such as pancreatic, brain and gastric cancers, with a relative risk of 3.5 in acute leukemias [3]. Among the leukemias, the highest incidence is found in acute promyelocytic leukemia (APL), by as much as 3.5 to fivefold in three studies including a total of 1553 patients [4–6]. VTE adds to the comorbidity in leukemic patients and also adversely affects survival [7].

Bleeding is also a well-recognized complication of acute leukemia. The overall incidence of bleeding in thrombocytopenic patients was found to be as high as 58.4% [8]. However, the incidence of clinically significant bleeding, which includes WHO grade 2 (melena, hematemesis, hematuria or hemoptysis), WHO grade 3 (bleeding requiring transfusion) and WHO grade 4 (retinal, cerebral or fatal bleeding), was 14.5, 6.9 and 3.2%, respectively. Factors that increase the risk of bleeding include thrombocytopenia, endothelial injury, fibrinolysis, acquired hemophilia and the adverse effects of drugs. In this article, we will outline the incidence, pathogenesis and management of thrombosis and bleeding in acute leukemia.

Thrombosis

Thrombotic complications in acute leukemia can occur in any part of the body but often show site-specific predilections. This is especially notable in acute lymphoblastic leukemia (ALL) in children, where the incidence of thrombosis is 1.7–36.7% [9,10], averaging 5.2% [11]. The incidence depends on the choice of chemotherapeutic agents and the use of central venous access catheters. Remarkably, among the sites of thrombosis, approximately half (53.8%) occurred in the CNS, most commonly as sino-venous thrombosis, with cerebral infarction in 9.9%.

Although ALL is less common in adults, a similar incidence of thrombosis of 5.9% is seen. In contrast to childhood ALL, deep-vein thrombosis in adults originates in the lower limbs in 38.9% of this complication [12]. In ALL, two major factors of thrombosis are the presence of a central venous catheter and the use of treatment protocols containing L-asparaginase. This drug inhibits the synthesis of both coagulant and anticoagulant proteins in the liver. However, following the cessation of L-asparaginase therapy, the

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recovery of anticoagulants, especially antithrombin, lags behind the recovery of the coagulant factors, leading to an increased risk of thrombosis [9,13–15].

Pathogenesis

The classical view for the pathogenesis of thrombosis is based on Virchow's triad of aberrant blood flow, disruption of vessel integrity and altered components in blood [16]. The current concept has expanded on this triad (Box 1). In acute leukemia, aberrant blood flow is often appreciated in the setting of hyperleukocytosis. This can lead to leukostasis and the development of hyperviscosity syndrome. Vascular integrity is disrupted with the need for multiple blood draws and invasive procedures such as placement of central venous access catheters. It is less recognized that vascular injury also occurs when there is leukemic infiltration of the endothelial lining. This will lead to endothelial cell activation and increased expression of proinflammatory and proangiogenic cytokines. The inflammatory cytokines, TNF-α and IL-1β, stimulate the production of procoagulants such as tissue factor (TF), von Willebrand factor and the antifibrinolytic factor, plasminogen activator inhibitor type 1 (PAI-1). In addition, leukemic cells express TF and a cancer procoagulant, releasing these factors into the circulation as microparticles.

In leukostasis, obstruction to blood flow starts in the microcirculation, particularly in the brain, eyes, myocardium, lungs and kidneys, and may progress to multiple organ failure. Initial manifestations are headache, dizziness, visual changes, chest pain and shortness of breath. Mortality rate is high, especially when there is involvement of both the brain and lungs [17]. Leukostasis develops when there is hyperleukocytosis – defined as a peripheral blast count exceeding 100,000/μl. The frequency of hyperleukocytosis ranges from 5 to 13% in adult acute myelogenous leukemia (AML) and 12 to 25% in pediatric AML [17–19]. Acute leukemia with monocytic differentiation (French–American–British classification: M4 and M5) often presents with leukostasis as a significant complication [20]. Nearly 40% of patients presenting with poorly differentiated monoblastic leukemia have white blood cell counts greater than 100,000/μl at diagnosis [21]. The microgranular variant of APL and acute myelomonocytic leukemia with atypical eosinophils may also present with hyperleukocytosis [22,23]. Chromosomal abnormalities, most consistently 11q23, have also been associated with hyperleukocytosis and leukostasis [24]. Myeloblasts, especially in the M4 and M5 subtypes, are larger and less deformable than in other subtypes, and thus leukostasis occurs more frequently. This picture is often seen in AML in infants as the leukemia is often myelomonoblastic (M4) or monoblastic (M5), and shows high blast counts [25]. There is usually a significant tumor burden with hepatosplenomegaly and CNS involvement, the latter probably due to leukostasis.

Box 1. Thrombosis in acute leukemia: present-day concept of Virchow's triad.

Aberrant blood flow

- Hyperleukocytosis and leukostasis

Vascular injury

- Cytokines
  - Proinflammatory: IL-1β, TNF-α and MCP-1
  - Proangiogenic: IL-8 and VEGF
- Endothelial cell activation
  - P-selectin, E-selectin, PECAM-1, ICAM-1 and VCAM-1
- Leukemic infiltration
- Endothelial injury from vascular access catheters

Altered components of blood

- Increased procoagulants
- Increased inhibitors of fibrinolysis (PAI-1)
- Factors produced by leukemic cells: tissue factor, cancer procoagulant and factor V receptor

MCP: Monocyte chemoattractant protein; PAI-1: Plasminogen activator inhibitor type 1; PECAM: Platelet endothelial cell adhesion molecule.

The cause of leukostasis was previously thought to be due to hyperleukocytosis and increased blood viscosity. However, this concept was recently challenged. Whole-blood viscosity is affected only when the leukocrit reaches 12–15%, corresponding to a white cell count of 300,000–450,000/μl in AML and 600,000–800,000/μl in ALL. However, clinical leukostasis frequently manifests at a lower white cell count. Thus, other factors have to be taken into consideration. It is now generally believed that the adhesive molecules in both the endothelium and leukemic blasts play an essential role. *In vitro* studies showed an increased expression of adhesive molecules by endothelial cells and corresponding receptors in the myeloblasts [26]. Myeloblasts, through their production of cytokines, including TNF-α and IL-1β, were found to upregulate the expression of ICAM-1, VCAM-1, P-selectin and E-selectin by endothelial cells. At the same time, their corresponding receptors, such as CD11b, are present in the myeloblasts. In such a microenvironment, the endothelial cells are able to recruit myeloblasts, forming a vicious cycle where more cells are trapped, leading to leukostasis. In the M4 and M5 subtypes of AML, CD11b, a receptor of ICAM-1 and ICAM-2, is highly expressed in the myeloblasts, whereas in the M0, M1, M2 and M3 subtypes, there is less expression of this receptor, thus providing another reason for the higher frequency of leukostasis in the M4 and M5 subtypes. This new concept has significant implications in the management of this complication.

The optimal method for management of leukostasis was formerly thought to be cytoreduction by both leukapheresis and chemotherapy. This was based on the belief that by lowering the peripheral blast count, leukostasis may resolve. This concept is now being challenged. As discussed earlier, hyperleukocytosis is playing a much less significant role than previously thought. A recent study of 48 patients showed that the reduction of the white cell count had no significant effect on early death or survival [27]. Thus, prompt initiation of chemotherapy is essential. Other measures, including high doses of corticosteroids, should also be considered. Corticosteroids are known to block the upregulation of the adhesion glycoprotein CD18, L-selectin and IL-8 receptors in myeloid cells *in vitro*. This beneficial effect of corticosteroids can reduce leukostasis. Retrospective studies have shown that hyperleukocytosis is a predictor of poor overall survival and of early death.

Although leukapheresis did not improve overall survival [17,28], it is still being commonly practiced. It has a potential benefit of rapid removal of the myeloblasts and reducing the risk of tumor lysis syndrome.

Disruption of vessel integrity

Sinusoidal obstruction syndrome, formerly known as hepatic veno-occlusive disease, is a good example of site-specific vascular endothelial damage leading to thrombosis [29,30]. The microcirculation in zone three of the hepatic acinus is occluded by edema, red cell extravasation and fibrin deposition. Thrombosis of the hepatic central vein occurs in 55% of mild cases and 75% of severe cases. The pathogenesis is believed to be endothelial damage from toxins and chemicals, and is seen in patients receiving chemotherapy or radiation used in myelo-ablative therapy for bone marrow transplantation [31]. Implicated chemotherapeutic agents include gemtuzumab ozogamicin (Mylotarg® [Pfizer Inc., NY, USA]), actinomycin D, dacarbazine, cytosine arabinoside, mitramycin, 6-thioguanine and urethane. Nonchemotherapeutic toxins include the plant alkaloid pyrrolizidine, found in the *Boraginacaea* family, which is often used in herbal tea and other herbal medicines. Anticoagulants are not effective. A polydisperse oligonucleotide defibrotide has been found to offer some benefit [31].

Acute promyelocytic leukemia

This subtype of acute leukemia has distinct molecular, morphologic and clinical characteristics that set it apart from other types [32,33]. It also has a high incidence of thrombotic and bleeding complications. Differentiation of the granulocytic lineage is blocked at the stage of promyelocytes. This can be reversed by treatment with all-*trans* retinoic acid (ATRA) and/or arsenic trioxide (ATO), making APL the paradigm of differentiation therapy [34]. The microgranular variant occurs in 20% of cases and presents with leukocytosis instead of the leukopenia typical of the classic form [35,36]. Patients with thrombocytopenia and a high leukemic cell count have a worse prognosis [37]. Complete remission can be achieved with a combination regimen of a differentiating agent (ATRA or ATO) and chemotherapy in over 90% of patients [38]. However, the early mortality rate remains high, primarily due to the high incidence of bleeding and thrombotic complications [39–41]. APL patients frequently present with bleeding. Most patients have varying degrees of laboratory abnormalities in their coagulation parameters. The overall picture is one of disseminated intravascular coagulation (DIC), with prolonged prothrombin time, partial thromboplastin time and thrombin time, and with increased levels of fibrinopeptide A, prothrombin fragment 1+2, fibrin degradation products and D-dimer. The fibrinogen level and the platelet count are decreased [42–44]. Fibrinolytic abnormalities are also present with increased tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA), decreased PAI-1 and decreased α2-antiplasmin [44–48]. These changes are reversed 4–7 days following treatment with ATRA [42,44,48]. Thus, it is imperative that ATRA is initiated as soon as the diagnosis of APL is suspected. Of the bleeding complications, 65–80% are intracranial hemorrhages (ICHs), usually fatal, followed by gastrointestinal bleeding and pulmonary intra-alveolar hemorrhage [49,50]. Paradoxically, thrombosis is also a major complication, creating a double hazard in this disorder [51–55]. Thrombosis occurred in 12% of cases in one series [56], and in 15–25% of patients in a post-mortem study [57]. APL with the molecular features of the bcr3 isoform, which expresses CD2, CD15 and FLT3-ITD, is associated with a higher incidence of thrombotic complications [55]. Portal vein thrombosis may occur in the microgranular variant expressing CD2 [58]. Thrombosis can also be seen complicating the differentiation syndrome (formerly known as retinoic acid syndrome or ATRA syndrome) [59].

The hemostatic balance in APL is usually severely perturbed (Figure 1). This is caused by multiple factors, including varying degrees of thrombocytopenia, increases in procoagulant activities of the leukemic promyelocytes, and changes in the plasminogen-plasmin system. Many of the increased procoagulant activities originate from the leukemic promyelocytes. *In vitro* studies showed that the human promyelocytic leukemia cell line NB4 expresses high levels of TF [60] and cancer procoagulant [60]. TF is the physiologic initiator of the coagulation activation cascade in both healthy individuals and in malignant tissue [61]. The procoagulant activity of TF on normal cell surfaces is largely dormant until alterations of the plasma membrane occur. Thus, disrupted cells and apoptotic cells generate more procoagulant activity than intact cells [62]. TF expression is increased in APL promyelocytes. The procoagulant activity of lysates from freshly isolated APL cells is mainly attributed to TF, while CP only exerts a minimal effect. APL cells may also induce TF procoagulant activity of endothelial cells through their secretion of IL-1β. Thus, during periods of increased apoptosis of promyelocytes during treatment of APL, the procoagulant activity is correspondingly intensified. There is a high rate of promyelocyte turnover with increased apoptosis at the onset of treatment. The apoptosis is then further enhanced by treatment with ATO or chemotherapy. As the leukemic cells undergo apoptosis, exteriorization of the phospholipids, especially phosphatidylserine, on the cell surface leads to activation of TF. Thus, apoptotic cells are more thrombogenic [63]. This may explain the clinical observations in the pre-ATRA era that bleeding manifestations were exacerbated during chemotherapy.

In addition, there is an alteration in the physiologic balance between profibrinolytic and antifibrinolytic factors in APL. Fibrinolytic activity is increased in several scenarios. A secondary fibrinolysis can occur as a response to DIC. Second, the leukemic promyelocytes overexpress both tPA and uPA. In addition, annexin A2, a coreceptor for plasminogen and tPA, was found to be highly expressed in the APL promyelocytes and in NB4 cells [64]. The expression of these factors is downregulated after ATRA. Overall, there is an increase in the fibrinolytic activity at presentation. It is uncertain how much this can counteract the procoagulant activity in the clinical setting. At the least, fibrinolytic activity is a major factor in bleeding complications. In addition, the preponderance of intracranial bleeding in APL may be explained by a higher expression of annexin A2 in the microvascular endothelial cells in the brain when compared with endothelial cells elsewhere [65]. Such high expression of this receptor of plasminogen and tPA

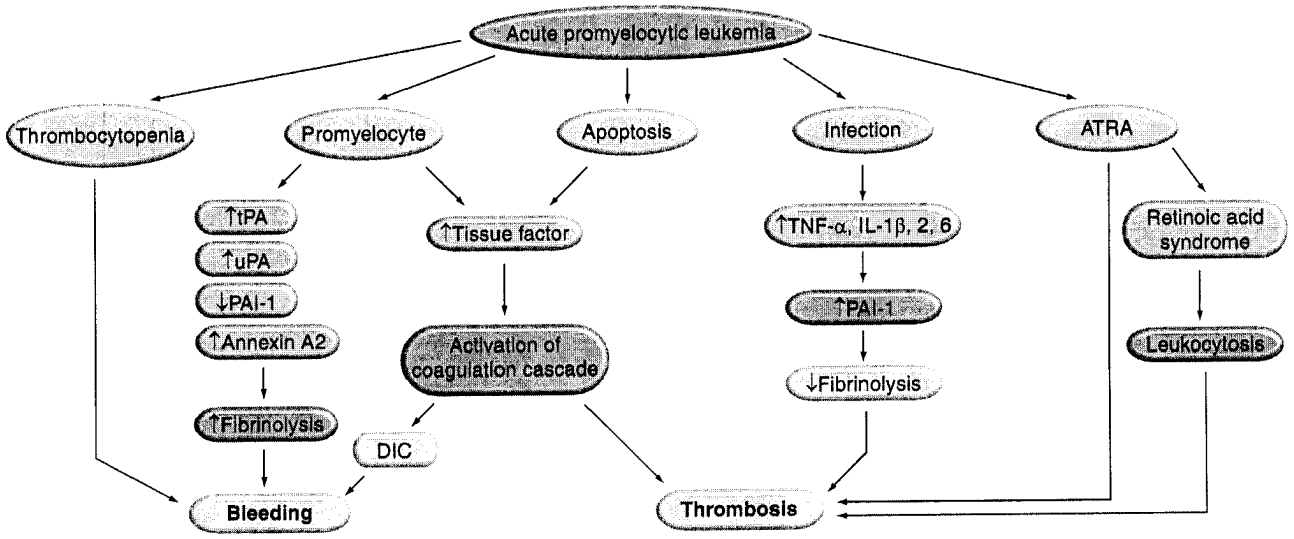

Figure 1. Hemostatic dysfunction in acute promyelocytic leukemia showing the respective mechanisms described in the text.
ATRA: All-*trans* retinoic acid; DIC: Disseminated intravascular coagulation; PAI-1: Plasminogen activator inhibitor type 1; tPA: Tissue plasminogen activator; uPA: Urokinase plasminogen activator.
Modified with permission from [132].

localizes plasmin generation in the microvasculature of the brain. In the presence of annexin A2, plasmin generation is increased by as much as 60-fold [65]. Since annexin A2 is highly expressed in leukemic promyelocytes, the degree of fibrinolysis is proportional to the leukemic burden. This is supported by the observation that severe bleeding complications are correlated with the white cell count [56]. On the other hand, the antifibrinolytic factor PAI-1, is upregulated in APL [44]. PAI-1 is a potent inhibitor of tPA and uPA. The increase in PAI-1 is variable and dependent on several factors. Inflammatory cytokines, especially TNF-α and IL-6, upregulate the expression of PAI-1 [66]. Thus, in the presence of infection or sepsis in APL, the PAI-1 level is increased. Conversely, leukocyte elastase and other proteases from the leukemic promyelocytes degrade PAI-1 into an inactive form [46], resulting in decreased PAI-1 activity in the plasma. Thus it is not surprising to see contradictory findings in the literature when the data are not analyzed according to the status of infection or the severity of the DIC. The abnormal PAI-1 levels return to normal with ATRA [44,67].

Although hypercoagulability is a major underlying cause of the bleeding and thrombotic complications of APL, the use of anticoagulants is not effective. In the past, heparin was commonly used to control coagulopathy. However, a retrospective study conducted in the pre-ATRA era comparing the benefits of heparin and antifibrinolytic agents found no benefit for either approach [39]. In the study of the Spanish Cooperative Group, Programa para el Estudio de la Terapéutica en Hemopatías Malignas, the addition of a prophylactic dose of tranexamic acid failed to reduce the incidence of ICH [68]. In the absence of prospective clinical trials, the current guidelines by experts [69,70] are based on clinical findings and the present understanding of the pathogenesis. First, the coagulopathy is readily controlled by differentiating agents (ATRA or ATO). Thus initiation of these agents should be carried out as soon as the diagnosis of APL is considered, prior to the molecular confirmation. Second, since thrombocytopenia is associated with worse bleeding, the platelet count should be maintained at the level of at least 30,000/μl. Bleeding in the presence of DIC should be treated by replacement of clotting factors with fresh frozen plasma, and fibrinogen levels should be maintained above 150 mg/dl by cryoprecipitate and viral-free fibrinogen preparations. Heparin is not recommended, as it is ineffective and may cause more bleeding. Prior to the advent of ATRA, chemotherapeutic induction was associated with increased bleeding. This can be explained by increased apoptosis of the leukemic promyelocytes induced by chemotherapy, leading to a surge in release of TF from apoptotic cells. More TF increases the severity of DIC-associated bleeding. Chemotherapy should not be started without concurrent treatment with ATRA or ATO. Aggressive treatment should be carried out in cases of infection, as inflammatory cytokines cause increased procoagulant activities.

Contribution of inherited & acquired thrombophilia

Hereditary deficiency of antithrombin, protein C or protein S carries the highest additional risk of thrombosis, followed by factor V Leiden and prothrombin G20210 mutation [71]. By contrast, among the acquired thrombophilia, antiphospholipid syndrome is the most significant. Although rare in acute leukemia [72], it deserves attention because the rate of thrombosis among those with antiphospholipid syndrome is approximately 32% [73]. The levels of antiphospholipid antibodies decrease after treatment of the malignancy.

Iatrogenic complications

Catheter-related deep vein thrombosis

Infection and thrombosis are the two most frequently encountered complications of central venous catheters [74,75]. As the catheter is made of nonbiologic material, a sheath composed of fibrin and platelets is quickly formed after placement [76,77]. This is usually asymptomatic and readily replaced with collagen covered by regenerating endothelial and smooth muscle cells. The process can cause malfunction of the catheter, manifesting as: failure to withdraw blood, caused by the fibrin sheath forming a ball-valve or by an intraluminal thrombus; upper limb venous thrombosis, caused by peri-catheter thrombus extension; and signs of infection or sepsis, due to microorganisms seeding the catheter tip. The incidence of catheter-related deep vein thrombosis (CRDVT) in earlier studies was believed to be high, with a prevelance as great as 30–74%, with a wide range depending on the methods of diagnosis and duration of catheter placement [78,79]. More recent prospective studies indicate a much lower incidence of 3–6% [80,81]. Most are asymptomatic [82]. Pulmonary embolism occurs in 9–16% of CRDVT [83,84]. Several prospective studies with prophylactic low-molecular-weight heparin showed no benefit [85,86]. A recent survey of 1761 patients with CRDVT confirmed that prophylactic anticoagulation is not effective [87]. Thus, prophylaxis is not recommended [88]. Although there are no evidence-based data, one author recommends prophylaxis in patients with a prior history of unprovoked (idiopathic) VTE [89]. Upon development of CRDVT, therapeutic anticoagulation was not predictive of thrombus resolution. In the above survey, removal of the catheter was found to be the only method showing benefit. There are no data that show an increased risk of embolization by catheter removal, and thus it should be performed [87]. Systemic thrombolytic therapy had been used but found to be associated with a high rate of bleeding [90]. Catheter-directed thrombolysis has been observed to result in partial resolution of the thrombus [91,92]. More clinical trials are needed to verify the benefits of this approach.

Adverse effects of drugs

In recent years, the thrombogenic effects of drugs used in the treatment of acute leukemia have been recognized and more closely monitored [93].

L-asparaginase

This drug proteolyses the amino acid L-asparagine, which is essential for cell growth. While normal cells contain L-asparagine synthetase and are, thus, self-supporting, leukemic and lymphoma lymphocytes do not. This enzyme is used in the treatment of ALL and lymphoma. Unfortunately, it inhibits hepatic synthesis of proteins involved in coagulation and fibrinolysis. These proteins include the procoagulants (fibrinogen, and factors V, VII, IX, X and XI) and the anticoagulants (antithrombin, protein C and protein S). They also include the profibrinolytic protein plasminogen and the antifibrinolytic proteins α2-antiplasmin, α2-macroglobulin and histidine-rich glycoprotein. This may lead to an increased risk of bleeding during L-asparaginase therapy. The incidence of bleeding is low unless there is concurrent vascular injury. In many treatment regimens for ALL, corticosteroids are first administered for 4–5 days. This produces a moderate reduction in plasma fibrinogen levels. Following this, as L-asparaginase is given, the hypofibrinogenemia is amplified. The plasma fibrinogen level provides a valuable clinical guide to the bleeding risk. There are two prospective nonrandomized trials of prophylactic use of fresh frozen plasma, showing that there are no benefits on hemostasis [94,95]. However, when the fibrinogen level falls below 100 mg/dl, the current standard practice is to administer cryoprecipitate or viral-free fibrinogen preparations as replacement therapy. Additional platelet replacement is indicated if the platelet count falls to the recommendation threshold of 10,000/μl [96]. An entirely different situation occurs when L-asparaginase treatment is stopped. The hepatic synthesis of these products resumes, but the recovery of these proteins occurs at uneven rates. The procoagulants precede the anticoagulants, particularly antithrombin, and a brief period of hypercoagulability occurs. Plasminogen returns slower than the coagulants, with reduced fibrinolytic potential. A recent prospective study in childhood ALL treated with L-asparaginase showed an incidence of thrombosis of 37% [97]. The prophylactic use of antithrombin concentrate resulted in a reduced incidence of 28%. The site of thrombosis is often cerebral veins, causing encephalopathy and seizures [98]. Anticoagulant therapy along with antithrombin replacement may be indicated. However, there are no available data on the use of antithrombin in adults. In the event of venous thrombosis elsewhere, if thrombolytic therapy with a plasminogen activator, such as tPA, is considered, plasminogen supplementation would be required [99].

Erythropoietin-stimulating agents

Thromboembolic complications are a significant adverse effect with erythropoietin-stimulating agents for anemic patients. In a meta-analysis of 6769 cancer patients treated with epoetin or darbopoetin, thromboembolic events occurred in 229 out of 3728 cancer patients treated with erythropoietin, compared with 118 out of 3041 control patients [100]. These cancer patients included those with acute leukemia, but were not analyzed as a separate group. *In vitro* studies showed erythropoietin receptors are present in most tumor cells and the use of erythropoietin-stimulating agents may stimulate proliferation [101]. This led to a warning from the US FDA against their use in cancer patients. In acute leukemia, *in vitro* studies showed the erythropoietin receptor is overexpressed in leukemic cell lines with t(12;21)(p13;q22) with its molecular counterpart, the *ETV6/RUNX1* (also known as *TEL/AML1*) fusion gene [102]. Erythropoietin may also stimulate proliferation of these leukemic cells. *ETV6/RUNX1* is present in 25% of childhood pre-B-cell ALL.

Other growth factors

Thrombotic events have been described in cancer patients receiving granulocyte colony-stimulating factor (G-CSF; Neupogen® [Amgen Inc., CA, USA]) or granulocyte macrophage colony-stimulating factor (GM-CSF; Leukine™ [Immunex Corp., WA, USA]) [103] with an incidence of 2.8% (4.2% with GM-CSF and 1.2% with G-CSF). The incidence in patients undergoing chemotherapy for stem cell transplantation was also higher with GM-CSF (9.8%) than with G-CSF (2.3%). G-CSF has been

found to activate coagulation, increasing factor VIII levels, thrombin–antithrombin complexes and prothrombin fragment F1+2 in allogeneic stem cell donors [104]. G-CSF also increases TF antigen and activity in donors [105]. Although these findings are not sufficient to warrant prophylactic anticoagulation, there should be an increased awareness when growth factors are used.

Glucocorticoids

The association between excessive corticosteroids and thrombosis was first observed in Cushing's syndrome. Increased plasma levels of prothrombin, von Willebrand factor and antithrombin, along with decreased fibrinogen and plasminogen, are observed in glucocorticoid therapy [106]. Glucocorticoids mediate apoptosis in tumor cells, including leukemic cells [107]. This agent is included in most chemotherapeutic regimens. When used with thrombogenic drugs, such as thalidomide, glucocorticoid results in a much higher incidence of thrombosis. In one study, high-dose dexamethasone in childhood ALL was found to be associated with a lower rate of thrombosis [108], but this association was not verified in a recent meta-analysis [11]. The thrombogenic potential of corticosteroids is often under-recognized. In certain conditions, such as hyperleukocytosis, the potential benefit of steroids may outweigh this thrombogenic risk.

All-trans retinoic acid

All-*trans* retinoic acid in APL results in a rapid downregulation of TF in APL promyelocytes and normalization of coagulation changes in blood within 4–5 days. It is paradoxically associated with thrombotic complications later in the course of the illness, 1–3 weeks following initiation of therapy [53,54,59]. The risk of thrombosis is increased when antifibrinolytic agents (tranexemic acid or ε-amino-caproic acid [Amicar®, Xanodyne Pharmaceuticals Inc., KY, USA]) are used [109,110]. As these agents have not been shown to be effective in controlling bleeding in APL, they are contraindicated. The thrombosis seen with ATRA is distinct from another complication associated with this drug, the differentiation syndrome [111–113]. In this syndrome, there is an interstitial infiltrate of maturing myeloid cells into the pulmonary alveoli. Corticosteroids have been shown to be effective in the prevention and treatment of this complication.

Gemtuzumab ozogamicin (Mylotarg)

This is an immunoconjugate of anti-CD33 monoclonal antibody with calicheamicin, and has been used in the treatment of AML with CD33-positive myeloblasts, especially in elderly patients. A serious side effect is sinusoidal obstruction syndrome, which occurs in up to 28% of patients if given with thioguanine [114]. It has recently been withdrawn from the market by the FDA.

Bleeding

Bleeding is a common occurrence in acute leukemia. Most patients have bleeding over the course of their leukemia. In childhood ALL, hemorrhage is a major cause of death, with two-thirds of the hemorrhagic mortality due to ICH [115,116]. Likewise, in APL, ICH is the most common site of bleeding (80%), followed by gastrointestinal bleeding and pulmonary intra-alveolar hemorrhage. Factors associated with bleeding include thrombocytopenia, endothelial injury, excessive fibrinolysis, acquired hemophilia and adverse effect of drugs commonly used in the treatment of acute leukemia (Box 2).

Thrombocytopenia

This is the most frequently encountered cause of bleeding in acute leukemia. Although it may not be the sole cause of bleeding, correcting thrombocytopenia will reduce the bleeding risk in most patients. However, platelet transfusion is not an entirely innocuous procedure. The incidence of complications is relatively low. Owing to the need to store platelets at room temperature, bacterial contamination occurs in one out of 1000 to one out of 3000 transfused units [117]. It is often under-recognized and underreported because recipients of the contaminated product may be asymptomatic or experiencing a transient febrile episode. Sepsis is less common, with a rate of between one in 13,000 and one in 100,000, and a fatality rate of one in 17,000 with pooled platelets and one in 61,000 with apheresis platelets [117,118]. Another serious complication of platelet transfusion is transfusion-related acute lung injury [119,120]. This occurs within 6 h of transfusion and is due to injury of the pulmonary microvasculature with capillary leak, caused by activated leukocytes [121]. A significant complication is the development of alloimmune platelet refractoriness. This is frequently seen in patients who require long-term platelet transfusions. Leukocyte reduction in the platelet product decreases the incidence of this complication. When alloimmune platelet refractoriness develops, it should be managed by using HLA-compatible apheresis platelets [122].

Consideration of adverse effects of platelet transfusions, the expense and limited supply led to guidelines on the indications of platelet transfusions. Active major bleeding is a clear cut indication for therapeutic platelet transfusions. However, there are controversial issues in giving platelets to a thrombocytopenic patient prophylactically. Many earlier controversies are related to the platelet count threshold, dose of platelets and type of platelets. They have been clarified by recent clinical trials (Box 3). Evidence-based guidelines have indicated a few issues are still controversial [123]. As a result of multiple clinical trials, the platelet threshold is now established to be 10,000/μl, except in the case of preparations for invasive procedures or the presence of intracranial lesions [96]. While

Box 2. Causes of bleeding in acute leukemia.

- Thrombocytopenia
- Vascular injury: leukostasis, radiation, invasive procedures
- Coagulopathy: acquired von Willebrand's disease, acquired hemophilia, renal and liver dysfunction, nutritional deficiency
- Excessive fibrinolysis – increased tPA, uPA and annexin A2 in leukemic cells
- Adverse effect of drugs

tPA: Tissue plasminogen activator; uPA: Urokinase plasminogen activator.

both whole-blood-derived platelet concentrates (obtained from 4–6 units) and apheresis platelets are available, there are no strict guidelines as to the preference [124]. The latter product has the advantage of a decreased rate of bacterial contamination but is more costly. The effective dose of platelets in preventing bleeding has recently been studied in a randomized clinical trial [125]. No difference was found in the bleeding rates among the three doses studied (1.1×10^{11}, 2.2×10^{11} and 4.4×10^{11} platelets per m^2). The results support the outcome of earlier trials [126].

The clinician may use several measures to monitor the effect of platelet transfusions [127,128]. Platelet count increment, measured by the 1-h post-transfusion platelet count, is useful but can be affected by fever, infection, splenomegaly, bleeding, lymphocytotoxic antibody-positivity, transfusion reactions, disseminated intravascular coagulation, and the use of amphotericin, heparin and intravenous γ-globulin [129].

Autoimmune coagulopathy

Acquired hemophilia is an autoimmune disorder with the presence of an IgG autoimmune antibody against factor VIII. It is rarely seen in acute leukemia, but can occur in chronic lymphocytic leukemia [130].

Adverse effects of drugs

Patients with acute leukemia need to be monitored closely while on anticoagulant or antiplatelet therapy. Anticoagulant medications, including heparin, foundaparinux, enoxaparin, dalteparin and warfarin, can increase the risk of bleeding in acute leukemia. Antiplatelet agents including acetylsalicylic acid, clopidogrel, eptifibatide, abciximab and dipyridamole also increase the severity of clinically significant bleeding, particularly in the setting of thrombocytopenia. Typically antiplatelet or anticoagulant therapy is held once platelet levels are less than 50,000/μl. Indications for antiplatelet or anticoagulant therapy are important to consider when determining whether or not to discontinue these medications. Frequent consultation with cardiology or neurology specialists will be necessary to determine the risk of stopping anticoagulation or antiplatelet therapy.

Vascular injury

Patients with acute leukemia experience bleeding complications due to vascular injury. One obvious cause is the frequent blood draws in the setting of thrombocytopenia. The risk of bleeding through this mechanism can often be minimized with the use of central venous catheters. Other significant bleeding risks include invasive procedures and chemotherapy. Chemotherapy-induced thrombocytopenia and mucositis are important contributory factors for this increased risk. Lethal bleeding complications were found in 10% of patients during the first month of chemotherapy [131].

Endothelial injury also occurs as previously discussed in the section on leukostasis. The same endothelial damage that causes leukostasis can also lead to clinically significant bleeding. The consequence of bleeding through this mechanism is most significant when it involves the CNS, but bleeding can occur in any organ system.

Box 3. Considerations when ordering prophylactic platelet transfusions.

- Platelet count threshold [96]
- Choice of product: whole-blood derived versus apheresis [124]
- Dose [125]
- Platelet increment [127,128]
- Platelet function monitoring [127,128]

Conclusion

With a better understanding of the pathogenesis of the thrombotic and bleeding complications in acute leukemia, many of the older concepts are being challenged. Better designs for clinical trials are now possible. As these complications are major causes of morbidity and mortality in acute leukemia, a better evidence-based approach is much needed for both their prevention and treatment.

Expert commentary

The patient with acute leukemia is faced with a double hazard of having a high risk of thrombotic as well as bleeding complications. This is better recognized today than it was in the past. Although much of the pathogenesis is still not fully understood, many contributory etiologic factors are now being recognized. In particular, iatrogenic factors, including adverse drug effects, are being closely scrutinized. There are distinct features of these complications in acute leukemia, particularly in APL. Awareness of these features is of considerable help in the diagnosis and management. Many of the current approaches are determined by evidence-based results of clinical trials. These resources are essential to form guidelines, as best exemplified in the case of platelet transfusion. Many more trials are needed to answer other issues.

Five-year view

The older concepts concerning the pathogenesis and management of thrombotic and bleeding complications in acute leukemia are being challenged. In 5 years' time, there will a better understanding of the role of vascular integrity in both the bleeding and thrombotic complications in acute leukemia. Many new risk factors will be identified, especially for ICH. More data on long-term follow-up of thrombosis in acute leukemia will be available. A better awareness of the iatrogenic adverse effects will lead to a change in procedures and safer drugs. New and safer anticoagulants and better and safer hemostatic drugs are being developed and will be available. Improved methods of management of thrombocytopenia will include better and safer platelet products. The role of thrombopoietic agents will be studied in the setting of bone marrow failures.

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Key issues

- Both thrombosis and bleeding are major complications in acute leukemia.
- Despite a significantly improved outlook for acute promyelocytic leukemia, thrombosis and bleeding are the major causes of death in the early period following diagnosis.
- Thrombosis can be site specific in acute leukemia, especially in childhood acute lymphoblastic leukemia.
- Leukostasis is more common in M4 and M5 acute myeloid leukemia. Athough leuko-reduction by apheresis is no better than by treatment with chemotherapy alone, this practice is still used.
- Thromboprophylaxis is not effective for catheter-associated deep vein thrombosis.
- Thrombocytopenia is a major cause of bleeding.
- New platelet transfusion guidelines define platelet threshold, preparation of platelets, dose and methods of monitoring the effects.
- Breach in the vascular integrity contributes to both thrombotic and bleeding risk.
- Comorbid conditions play an important role, especially infection.
- Drugs used in the treatment of acute leukemia can cause thrombosis and bleeding, a fact that is often under-recognized.

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