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STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Hematology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

Management of Bleeding Complications in Patients with Cancer

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INTRODUCTION

Patients with cancer can have many hematologic complications. One of the most serious is bleeding, which can range in severity from laboratory abnormalities to life-threatening hemorrhage. The bleeding can be due to complications of the cancer, its therapy, or treatment for complications of cancer such as thrombosis. This manual discusses an approach to the cancer patient with bleeding, with a specific focus on issues such as coagulation defects, thrombocytopenia, and platelet dysfunction. Bleeding complications of specific cancers and their treatment will be discussed as well.

EVALUATION OF THE BLEEDING CANCER PATIENT

Bleeding problems in patients with cancer can result from the malignancy itself due to either direct invasion of a vessel or as a paraneoplastic effect, as well as from the effect of antineoplastic treatment or from nonmalignancy–related factors. The first step in evaluation is to review the patient's oncology history, especially for recent therapy they may have received. For patients whose initial presentation of their cancer is a bleeding diathesis, attention should be directed to establishing the diagnosis (eg, abnormal forms on the blood smear suggesting leukemia, abnormal lymph nodes).

LABORATORY TESTING

The next step in evaluation is to obtain a basic set of coagulation tests. The prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), platelet count, and fibrinogen level should be rapidly obtained. Three patterns of defects can be seen in the PT/INR and aPTT (**Table 1**). Isolated elevations of the PT/INR are indicative of a factor VII deficiency. In very sick patients, low factor VII levels are also common due to third-spacing and increased consumption leading to an elevated INR.[1] High INR can also reflect hepatic synthesis defects due to liver metastasis. A marked elevation of the PT/INR out of proportion to the aPTT suggests vitamin K deficiency, perhaps due to poor oral intake. An isolated elevation of the aPTT has many causes, such as the presence of a lupus inhibitor or specific factor deficiency. Prolongation of both the INR and aPTT suggest multiple defects or deficiency of factors II, V, or X, and marked prolongation of the INR and aPTT can also be seen with low levels of fibrinogen.

If the platelet count is low, examination of the blood smear by the laboratory technician is essential to look for platelet clumping, which will falsely lower the platelet count. The smear also should be reviewed for schistocytes, the presence of which is a marker for thrombotic microangiopathies. In the absence of recent chemotherapy, the differential diagnosis for isolated profound thrombocytopenia (<10,000/μL) is generally limited to immune thrombocytopenia, drug-induced thrombocytopenia, or posttransfusion purpura.

Excessive bleeding has been reported with plasma fibrinogen levels lower than 100 mg/dL. The endpoints of the PT/INR and aPTT are timed to the formation of the fibrin clot. When plasma levels of fibrinogen fall below 80 mg/dL, the clot may be small and not detected by the machine, resulting in a very prolonged PT/INR and aPTT. Low fibrinogen levels reflect severe liver disease or consumptive coagulopathy.

Some bleeding disorders cannot be detected by routine laboratory tests, such as platelet function defects or increases in fibrinolysis. Performing rapid tests to assess platelet function remains controversial. The PFA100 is a rapid automatic test for platelet function that has replaced the bleeding time, but may not reflect platelet dysfunction due to patient use of drugs such as clopidogrel. Elevated values can be seen in patients with anemia, thrombocytopenia, and low fibrinogen level, and it also can be difficult to assess for excessive fibrinolysis. The euglobulin clot lysis time is a screen for fibrinolysis, but it is not standardized and can be difficult to obtain. Thromboelastography is a unique point-of-care laboratory test that examines whole blood thrombus formation and lysis, but it is not widely available and requires experience in interpretation.[2]

Table 1. Interpretation of Coagulation Test Results

Test Result	Potential Cause
Elevated PT, normal aPTT	Factor VII deficiency
	Vitamin K deficiency
	Warfarin
	Sepsis
Normal PT, elevated aPTT	Isolated factor deficiency (VIII, IX, XI, contact pathway proteins: XII, prekallikrein, high molecular weight kininogen)
	Specific factor inhibitor (same list as above)
	Heparin
	Lupus anticoagulant
Elevated PT, elevated aPTT	Multiple coagulation factor deficiencies
	Liver disease
	Disseminated intravascular coagulation
	Isolated factor X, V, or II deficiency
	Specific factor inhibitor
	High hematocrit (>60%, spurious)
	High heparin levels
	Severe vitamin K deficiency
	Low fibrinogen (<50–80 mg/dL)
	Dysfibrinogenemia
	Dilutional
	Dysproteinemia

aPTT = activated partial thromboplastin time; PT = prothrombin time.

COAGULATION DEFECTS

ACQUIRED VON WILLEBRAND DISEASE

Acquired von Willebrand disease (VWD) occurs most often in hematologic malignancies—lymphomas, myeloproliferative syndromes, myeloma, and monoclonal gammopathies—but can be seen with Wilms tumors and with the use of certain drugs such as ciprofloxacin.[3–5] The most common presentations are diffuse oozing from surgical sites, epistasis, or gastrointestinal bleeding.[6] Patients with acquired VWD can present with decreased total von Willebrand protein (type 1 VWD) or loss of high molecular weight multimers (type 2 VWD).[7]

The cancers most commonly associated with acquired VWD are lymphoproliferative disorders and myeloproliferative neoplasms. The types of myeloproliferative neoplasms that are associated with acquired VWD are polycythemia rubra vera and essential thrombocytosis, especially if the platelet count exceeds 1,000,000/µL. With extreme thrombocytosis, there can be loss of the high molecular weight multimers due to absorption by the platelets, leading to the type 2 form of VWD.

Patients with myeloproliferative neoplasms with platelet counts greater than 1,000,000/µL should be screened for acquired VWD, especially before they receive aspirin therapy or undergo major surgical procedures. Patients with other disease, especially lymphoproliferative disorders, should be screened if they have excess bleeding or bruising.

Patients with acquired VWD have variable responses to therapy for acute bleeding.[3,8,9] Desmopressin is effective in many patients with acquired VWD type 1 and type 2, but the magnitude and duration of effect are often reduced.[10] For bleeding patients, high doses of the antihemophilic factor/von Willebrand factor complex concentrate HumateP are indicated, with careful monitoring of levels.[11] For patients with very strong inhibitors that factor concentrates cannot overcome or severe, life-threatening bleeding, administration of recombinant factor VIIa may prove useful.[12]

ACQUIRED FACTOR VIII INHIBITORS

Factor VIII deficiency due to autoantibodies is the most frequently acquired coagulation factor deficiency complication in older cancer patients.[13,14] Unlike patients with congenital hemophilia, patients with acquired inhibitors often have ecchymoses covering large areas of their body and can have massive muscle and soft tissue bleeding. Patients will have prolonged aPTTs, a screening test for a factor inhibitor with a 50:50 mix that does correct, and a low factor VIII level. For severe or life-threatening bleeding, recombinant factor VIIa is the treatment of choice.[15] The dose is 90 µg/kg repeated every 2 to 3 hours until bleeding has stopped. Immunosuppression is used to eliminate the autoantibody. Steroids are first-line therapy, but often oral cyclophosphamide and rituximab are added. Ridding the patient of the inhibitor does not require successful tumor treatment and should be attempted before major procedures such as cancer resection are undertaken.[14]

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation (DIC) frequently complicates cancer. Simply stated, DIC is the clinical manifestation of inappropriate thrombin activation.[16] The activation of thrombin leads to:

- Fibrinogen conversion to fibrin
- Platelet activation and consumption
- Activation of factors V and VIII

- Protein C activation (and degradation of factors Va and VIIIa)
- Endothelial cell activation
- Excess fibrinolysis.

Although the initial process is the activation of the coagulation pathway, the depletion of platelets and factors, along with enhanced fibrinolysis, often leads to the patient presenting with bleeding, or hemorrhagic DIC. A unique form of DIC characterized by excessive fibrinolysis and high hemorrhage risk is seen in prostate cancer patients.[17] However, cancer patients can also present with a thrombotic phenotype with the classic Trousseau syndrome—the association of excess thrombosis in a cancer patient with DIC, a thrombotic DIC.[18,19]

Hemorrhagic DIC should be suspected if the patient presents with excessive bleeding either spontaneously or out of proportion to a procedure. The aPTT and PT are usually elevated in severe DIC but may be normal or shortened in chronic forms.[20] One may also see a shortened aPTT in severe acute DIC due to large amounts of activated II and factor X "bypassing" the contact pathway.

In thrombotic DIC, extensive blood clotting, both arterial and venous, is often seen and is frequently refractory to warfarin therapy. Patients may also have nonthrombotic endocarditis with multiple emboli.[19]

The platelet count can be reduced but may be normal in chronic DIC. Serum fibrinogen and platelets are decreased in acute DIC, but again may be in the "normal" range in chronic DIC.[21] The most sensitive of the basic screening test results for DIC is a decrease in the platelet count.[20,22] The fibrinogen level tends to fall below normal only in severe acute DIC.[20] Currently, the most specific test for DIC is the D-dimer level. When fibrin monomers bind to form a thrombus, factor XIII acts to bind their "D" domains together, creating a bond that is resistant to plasmin; this degradation fragment is known as the *D-dimer*. High levels of D-dimer indicate that thrombin has acted on fibrinogen to form a fibrin monomer that bonded to another fibrin monomer and this resulting thrombus was lysed by plasmin.

The best way to treat DIC is to treat the underlying cause, such as leukemia or prostate cancer.[16,17] However, factors must be replaced if depletion occurs and bleeding ensues. Management should be guided by the results from the complete blood count (CBC) and routine coagulation tests (**Table 2**).

Heparin therapy is reserved for the patient who has a thrombosis as a component of their DIC.[23] In rare cases where the patient requires frequent transfusions to replete factors, as can be seen with prostate cancer, one can judiciously use heparin to reduce the transfusion requirement. Specific heparin levels instead of the aPTT should be used to monitor anticoagulation.[23]

Table 2. Treatment of Disseminated Intravascular Coagulation

Hematocrit <21%	Administer red cells
Fibrinogen <150 mg/dL	Administer 10 units of cryoprecipitate
Platelets <50,000–75,000/μL	Administer 1 platelet pheresis concentrate or 6 to 8 packs of single donor platelets
Prothrombin time >INR 2.0 and aPTT abnormal	Administer 2 to 4 units of fresh frozen plasma

aPTT = activated partial thromboplastin time; INR = international normalized ratio.

DRUG-INDUCED HEMOLYTIC SYNDROMES

A severe variant of drug-induced immune complex hemolysis which may be associated with DIC has been recognized. Patients who receive certain second- and third-generation cephalosporins (especially cefotetan and ceftriaxone) may develop this syndrome, but it also has been reported with carboplatin and oxaliplatin.[24,25] The clinical syndrome associated with cephalosporin starts 7 to 10 days after administration of the drug, sometimes with just a single dose given as surgical prophylaxis. The patient will develop severe Coombs-positive hemolysis with hypotension and DIC. These patients are often believed to have sepsis and are often re-exposed to the cephalosporin, resulting in worsening of the clinical picture. The outcome is often fatal due to massive hemolysis and thrombosis.

Treatment of drug-induced hemolytic-DIC syndrome is anecdotal. Patients have responded to aggressive therapy, including plasma exchange, dialysis, and prednisone. Early recognition of the hemolytic anemia and the suspicion it is drug related is important for early diagnosis so that the patient is not rechallenged with the incriminating drug.

DISORDERS OF PLATELET NUMBER AND FUNCTION

THROMBOCYTOPENIA

Immune Thrombocytopenia

Immune thrombocytopenia (ITP) is a common condition affecting approximately 1:20,000 individu-

Table 3. Common Drugs Implicated in Thrombocytopenia in Cancer Patients

Antimicrobial
Amphotericin B
Methicillin
Piperacillin
Rifampin
Trimethoprim-sulfamethoxazole
Vancomycin
Anti-GP IIb/IIIa agents
H2-blockers
Cimetidine
Ranitidine
Acetaminophen
Carbamazepine
Heparin
Hydrochlorothiazide
Irinotecan
Nonsteroidal anti-inflammatory agents
Quinine

Information based on Aster and Bougie,[33] George et al,[36] and Arnold et al.[37]

als. ITP most commonly complicates the clinical course of patients with chronic lymphocytic leukemia, but can be seen with both Hodgkin and non-Hodgkin lymphoma as well as with solid tumors.[26,27] ITP occurs due to antibodies binding to platelet proteins, most often to the platelet receptor glycoprotein (GP) IIb/IIIa.[28] Patients may be asymptomatic or present with signs of bleeding and petechiae. Life-threatening bleeding is unusual. ITP can occur any time in the course of the neoplasm, from prior to the diagnosis to when the patient is years in remission.

There is no specific laboratory test that rules-in ITP; rather, it is a diagnosis of exclusion.[29] Extremely low platelet counts with a normal blood smear and a negative history can be diagnostic for ITP. It is important to question the patient carefully about all drug exposures, including over-the-counter medicines.

Therapy in ITP is guided by the patient's signs of bleeding and platelet counts. Overall, patients tolerate thrombocytopenia well. It is unusual to have life-threatening bleeding when platelet counts exceed 10,000/μL unless other sites of bleeding are present such as a gastrointestinal cancer. The primary therapy of ITP is corticosteroid therapy; for example, pulse dexamethasone 40 mg/day for 4 days.[30] In patients with severe thrombocytopenia (counts <10,000/μL) or active bleeding, 1 of 2 treatments can be tried for rapid induction of a response: intravenous immune globulin at 1 g/kg for 3 days or a single intravenous dose of anti-D antibody at 75 μg/kg—for patients with spleens who are Rh-positive; either therapy can induce a response in more than 80% of patients in 24 to 48 hours.[31,32] As with factor VIII inhibitors, the course of ITP is often independent of the course of the underlying tumor and treatment should be aimed at the ITP.

Drug-Induced Thrombocytopenia

Patients with drug-induced thrombocytopenia present with very low platelet counts, typically 1 to 3 weeks after starting a new medication.[33] In patients with a possible drug-induced thrombocytopenia, the primary therapy is to stop the suspect drug.[34,35] If there are multiple new medications, the best approach is to stop any drug that has been strongly associated with thrombocytopenia (**Table 3**).[33,36,37] Immune globulin and corticosteroids have been suggested as useful therapies in drug-related thrombocytopenia. However, since most of these patients recover when the agent is cleared from the body, therapy probably is not necessary and witholding therapy avoids exposing the patients to therapy-related adverse events.

Post-Transfusion Purpura

Patients with post-transfusion purpura (PTP) have the onset of severe thrombocytopenia (<10,000/μL), often with severe bleeding, 1 to 2 weeks after receiving blood products.[38,39] These patients are homozygous for minor platelet-specific antigens and have made antibodies to common platelet antigens, most commonly PLA1. For unknown reasons, exposure to the antigens from the transfusion leads to rapid destruction of the patient's own platelets. The diagnostic clue is thrombocytopenia in a patient, typically female, who was previously sensitized by exposure to fetal platelets during pregnancy and who has received a red cell or platelet blood product in the past 7 to 10 days. Treatment consists of intravenous immune globulin[40] and plasmapheresis to remove the offending antibody. If patients with a history of PTP require further platelet transfusions to treat bleeding, PLA1-negative platelets may be considered but are difficult to obtain.

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is both more common in cancer patients and associated with a higher rate of thrombotic complications.[41,42] HIT

occurs due to the formation of antibodies directed against the complex of heparin bonded to platelet factor 4, which can result in platelet and monocyte activation and can lead to thrombosis.[43] The frequency of HIT is 1% to 5% when unfractionated heparin is used but less than 1% with low-molecular-weight heparin. HIT should be suspected when there is a sudden onset of thrombocytopenia with either a 50% or greater drop in the platelet count from baseline or a decrease in the platelet count to less than 100,000/μL in a patient receiving heparin in *any* form. HIT usually occurs 4 to 10 days after starting heparin, but may occur suddenly in patients with recent (<3 months) exposure.[44–46]

The diagnosis of HIT can be challenging in the cancer patient who has multiple reasons for being thrombocytopenic. In this situation, laboratory testing for HIT is essential. Two forms of HIT tests exist. The current frontline testing is an enzyme-linked immunosorbent assay (ELISA) for the presumed pathogenic anti-platelet factor 4 antibodies. This test is very sensitive but not 100% specific, so positive results must be interpreted in the patient's clinical context. The other type of testing is a platelet activation assay where patient plasma, donor platelets containing radiolabeled serotonin (the serotonin-release assay), and heparin are combined. If added heparin induces platelet activation and release of serotonin, the test is considered positive. This test is both specific and sensitive but can be difficult to obtain rapidly. For a patient in whom the clinical probability of HIT is high, a positive anti-platelet factor 4 is diagnostic. For patients for whom there are multiple competing causes for their thrombocytopenia, a platelet aggregation test should be obtained to confirm the ELISA result.

The first step in therapy of HIT consists of stopping all heparin. Low-molecular-weight heparins cross-react with the HIT antibodies and therefore these agents are contraindicated.[47] Institution of warfarin therapy alone has been associated with an increased risk for thromboses.[44] For immediate antithrombotic therapy of HIT patients, the recommended agent is the direct thrombin inhibitor argatroban, but there is increasing experience with fondaparinux and the new direct oral anticoagulants (**Table 4**).[48–51] Patients with HIT should also be carefully screened for any thrombosis, including obtaining lower extremity Doppler ultrasonography, because of their propensity to have "silent" thrombosis.

Table 4. Treatment of Heparin-Induced Thrombocytopenia

Argatroban
Therapeutic: 2 μg/kg/min infusion with dose adjustments to keep aPTT 1.5 to 3 times normal. Decrease dose to 0.5 μg/kg/min in severe liver disease. For patients with multiorgan system failure, decrease dose to 1.0 μg/kg/min.
Fondaparinux
Prophylactic: 2.5 mg/day
Therapeutic: 7.5 mg/day (<50 kg, 5 mg/day; >100 kg, 10 mg/day)
Direct oral anticoagulants
Apixaban
Dabigatran
Rivaroxaban

THROMBOTIC MICROANGIOPATHIES

Thrombotic microangiopathies (TMs) such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremia syndrome (HUS) should be suspected when a patient presents with any combination of thrombocytopenia, microangiopathic hemolytic anemia (schistocytes and signs of hemolysis), and end-organ damage.[52] Patients with TMs can present with neurologic signs and symptoms, including headache, confusion, seizures, or strokes.

There is currently no rapid, widely available diagnostic test for the TMs, but rather an initial diagnosis is based on the clinical presentation.[53] Patients uniformly will have a microangiopathic hemolytic anemia with the presence of schistocytes on the peripheral smear. Renal insufficiency, and not frank renal failure, is the most common renal manifestation in TTP, with renal failure being seen in HUS. Thrombocytopenia may range from a minimal decrease in platelet number to platelets being undetectable. The lactate dehydrogenase (LDH) level is elevated and haptoglobin is low or undetectable in both TTP and HUS.

Untreated TTP is rapidly fatal. Mortality in the pre–plasma exchange era ranged from 95% to 100%. Today plasma exchange therapy is the cornerstone of TTP treatment and has reduced mortality to less than 20% in the classic form of the disease.[53–55] Most patients with TTP have an acquired deficiency of ADAMTS13 due to an autoantibody. Initiation of plasma exchange should not be delayed while waiting for ADAMTS13 results. Immunosuppression with corticosteroids and sometimes rituximab is started concurrently with plasma exchange to obtain long-term remissions.

TMs have a unique presentation in cancer patients, which is most often seen in patients with metastatic solid tumors. In these patients, the TM is due to widespread metastatic disease. The patient often has

evidence of metastasis in the bone marrow and lungs. Plasma exchange is ineffective in these patients, but resolution of the TM has been reported if the tumor is responsive to therapy. TMs can also occur in patients with lymphoproliferative disease, but in this setting the condition appears to be autoimmune and does respond to classic TTP therapy.

Therapy-Related Thrombotic Microangiopathies

TM syndromes can complicate treatment with a variety of therapies, including calcineurin inhibitors, mitomycin, and thienopyridines.[56] With calcineurin inhibitors, the TM occurs shortly after the agent is started, with the appearance of a falling platelet count, falling hematocrit, and rising LDH level.[57] Some cases have been fatal, but often the TM resolves with reduction of the calcineurin inhibitors dose or with a change to another agent.

In the past, TM was most commonly seen with the antineoplastic agent mitomycin C, with a frequency of 10% when a dose of more than 60 mg was used.[58] Currently, the most common antineoplastic drug causing TM is gemcitabine, with an incidence of 0.1% to 1%.[59–62] The appearance of the TM syndrome associated with gemcitabine can be delayed, and the condition is often refractory or fatal. Severe hypertension often precedes the clinical appearance of the TM.[63] The use of plasma exchange is controversial,[64] and there are reports of the use of the complement inhibitor eculizumab.[5]

TMs can complicate both autologous and allogeneic stem cell transplants.[65] The incidence ranges from 15% for allogeneic to 5% for autologous stem cell transplants. Several types of TMs are recognized in stem cell transplantations.[65,66] A "multi-organ fulminant" form occurs early (20–60 days), has multi-organ system involvement, and is often fatal. Another type of TM is similar to calcineurin inhibitor–associated TMs. A "conditioning" TM, which occurs 6 months or more after total body irradiation, is associated with primary renal involvement. Finally, patients with systemic cytomegalovirus (CMV) infections can present with a TM syndrome related to vascular infection with CMV. The etiology of stem cell transplant–related TM appears to be different from that of classic TTP since autoantibodies to ADAMTS13 have not been found in bone marrow transplant–related TTP. Some have implicated therapy-related vascular damage leading to the microangiopathy.[67] The therapy of stem cell transplant TM is uncertain. Patients should have their calcineurin inhibitor doses decreased. Although plasma exchange is often tried, response is poor with fulminant or conditioning-related TTP/HUS.[68]

HEMATOLOGIC CANCERS ASSOCIATED WITH BLEEDING

ACUTE PROMYELOCYTIC LEUKEMIA

Multiple hemostatic defects occur in patients with acute promyelocytic leukemia (APL).[69] Most, if not all, patients with APL have evidence of DIC at the time of diagnosis. Patients with APL have a higher risk of death during induction therapy when compared with patients with other forms of leukemia, most often due to bleeding. Unfortunately, outside of clinical trials the rate of early death in APL has not changed with the advent of new therapies.[70] Once in remission, APL patients have a higher cure rate than most patients with leukemia. APL is also unique among leukemias in that biological therapy with retinoic acid and arsenic is effective in inducing remission and cure in most patients.

APL patients can present with pancytopenia due to leukemic marrow replacement or with diffuse bleeding due to DIC and thrombocytopenia. Life-threatening bleeding, such as intracranial hemorrhage, may occur at any time until the leukemia is put into remission. The etiology of the hemostatic defects in APL is complex, and it is thought that they result from DIC, fibrinolysis, and the release of other procoagulant enzymes.[69,71] The diagnosis of APL can be straightforward when the leukemic cells are promyelocytes with abundant Auer rods, although some patients have the microgranular form without obvious Auer rods. Confirmation of a diagnosis of APL requires molecular testing to detect a translocation between chromosome 15 and 17, the t(15;17)(q22;q12), which results in the PML-RARA mutation. With the slightest suspicion of APL, a complete coagulation profile should be obtained, including PT/INR, aPTT, fibrinogen level, platelet count, and D-dimer level. Increasing fibrinogen levels tend to be a good marker of progress in treating the coagulation defects.

Therapy of APL involves treating both the leukemia and the coagulopathy. Currently, the standard treatment for APL is all-trans retinoic acid (ATRA) in combination with chemotherapy or arsenic.[72,73] This will induce remission in more than 90% of patients, and most of these patients will be cured of their APL. ATRA therapy will also lead to the early correction of the coagulation defects, often within the first week of therapy.[74] This is in stark contrast to the chemotherapy era when the coagulation defects would become worse with therapy. Rare reports of massive thrombosis com-

plicating therapy with ATRA exist, but the relationship to either the APL or ATRA is unknown. Given the marked beneficial effect of ATRA on the coagulopathy of APL and its low toxicity profile, it should be started empirically for any patients suspected of having APL while genetic testing is being performed.

Therapy for the coagulation defects consists of aggressive transfusion therapy support and possible use of other pharmacological agents to control DIC.[75] One should try to maintain the fibrinogen level above 150 mg/dL and the platelet count above 50,000/μL. Controversy still exists over the role of heparin in the treatment of APL.[76] Heparin use can lead to profound bleeding and should be avoided unless thrombosis is present.

OTHER LEUKEMIAS AND MYELODYSPLASTIC SYNDROMES

DIC can occur with acute leukemias other than APL. DIC can complicate the course of patients with myeloid leukemias, who present with high peripheral blast counts or after sudden cell lysis induced by intensive chemotherapy.[77] The second most common type of acute myeloid leukemia (AML) complicated by DIC is acute monocytic leukemia (M5), with 25% of patients found to have laboratory evidence of intravascular coagulation.[78–81] DIC has been reported in untreated chronic myeloid leukemia (CML)[82–85] and in acute lymphocytic leukemia (ALL).[86–88] When studied prospectively, DIC was seen in 12% of patients with ALL before chemotherapy, and this proportion rose to 78% during chemotherapy.[89]

Given this data, all patients presenting with leukemia should be screened for DIC and coagulopathy, hypofibrinogenemia, and severe thrombocytopenia before initiating therapy. Patients with subclinical DIC should be monitored during induction as cell lysis may rapidly cause overt DIC.

Multiple defects are found in the platelets of patients with myelodysplastic syndrome. These include reduced platelet aggregation in response to a variety of agonists and decreased platelet stores of von Willebrand protein and fibrinogen. Patients with myelodysplastic syndrome may have severe bleeding even with platelet counts above 50 x 10^9/L due to platelet dysfunction.

MYELOPROLIFERATIVE SYNDROMES

A higher incidence of bleeding is seen in many of the myeloproliferative syndromes, but the bleeding rarely results in major morbidity.[75,90] A quarter of patients with polycythemia vera experience some bleeding, but this is very rarely the cause of death. Most series report that 30% of patients with essential thrombocytosis have bleeding. Paradoxically, as noted above, the risk of bleeding appears to increase with platelet counts above 1,000,000/μL. The use of drugs that inhibit platelet function is associated with a higher incidence of bleeding. Patients with markedly elevated platelet counts will respond to lowering the counts to below 1,000,000/μL.[4] This can be done rapidly by plateletpheresis or (most frequently) with cytoreductive therapy such as hydroxyurea. Rare patients with myeloproliferative neoplasms will have an acquired factor V deficiency.[91] Symptomatic patients present with bleeding and elevated PT/INR and aPTT.

PLASMA CELL DYSCRASIAS

Plasma cell dyscrasias can affect many steps of the coagulation system and lead to severe bleeding.[92–94] Multiple coagulation abnormalities have been described in patients with plasma cell dyscrasias.[94] First, the physical structure of the fibrin clot may be abnormal due to increased serum globulins. Polymerization of fibrin is impaired in some patients with circulating light chains. Myeloma proteins have also been shown to inhibit the thrombin time in normal plasma. The site for factor XIII activity on fibrin strands can be blocked by an abnormal protein. The abnormal protein can bind to coagulation factors, leading to inhibition of factor function, especially of factor VIII. Finally, monoclonal proteins with specificity toward platelet GP IIb/IIIa have been reported. These patients may have mild to no thrombocytopenia but have a very severe bleeding diathesis.

Patients with systemic amyloidosis, either primary or that associated with myeloma, often demonstrate a marked increase in easy bruising and other bleeding symptoms.[95] The most common defect in coagulation testing of patients with amyloidosis is an elevation in the thrombin time, which is seen in 30% to 80% of cases.[96] An increased prothrombin time is seen in 20% to 24% of cases and an increased aPTT in up to 70%. Acquired factor X deficiency, most likely due to absorption of amyloid protein, can cause severe bleeding and prolong PT/INR and aPTT. Another cause of bleeding in patients with systemic amyloidosis is systemic fibrino(geno)lysis.[97] The mechanisms responsible for the fibrinolytic state are not known, but hypotheses include increased release of plasminogen activators, decreased plasminogen activator inhibitors, blood vessels infiltrated with amyloid, decreased levels of inhibitors of fibrinolytic enzymes because of adsorption onto amyloid fibrils, or perhaps amyloid liver disease. The use of fibrinolytic inhibitors such as ε-aminocaproic acid or

Table 5. Emergency Management of Platelet Alloimmunization

Evaluate for other causes of thrombocytopenia (heparin-induced thrombocytopenia, drugs)
Consider a platelet "drip" (1 unit of platelets given over 4–6 hours)
Consider antifibrinolytic therapy:
ε-aminocaproic acid 1 g/hr IV, or
Tranexamic acid 10 mg/kg every 8 hr

tranexamic acid has both corrected laboratory tests of fibrinolysis and reduced bleeding symptoms.[98]

Therapy for the hemostatic defects in the dysproteinemic syndromes includes removal of the offending protein, either by reducing the synthesis by treating the plasma cell dyscrasia with aggressive chemotherapy or by intensive plasmapheresis. As with with myeloma, treatment of the amyloidosis will correct the bleeding diathesis, and recurrence of bleeding can herald a relapse of the disease.

COAGULATION DEFECTS DUE TO THERAPY

Bleeding has been reported with the use of tyrosine kinase inhibitors in the treatment of CML, but it is unclear if this is due to the drug or underlying disease. Tyrosine kinase inhibitors have been reported to lead to in vitro platelet dysfunction, but for most patients this does not appear to be clinically significant.[99] Bleeding has also been reported with inhibitors of vascular endothelial growth factor.[100,101] Bevacizumab is associated with bleeding, especially after surgery or with treatment of squamous cell carcinoma of the lung. In these cases, the bleeding may be related more to lack of wound healing and tumor necrosis. The BTK inhibitor ibrutinib is associated with a 5% incidence of bleeding, including subdural hematomas, but the mechanism is unknown.[102]

THERAPY

PLATELET TRANSFUSIONS

Many cancer patients will develop thrombocytopenia due to either their underlying disease or chemotherapy. The low platelet count puts these patients at risk for bleeding, and it has been established that for an otherwise stable patient transfusing platelets when the platelet count is less than 10,000/μL will reduce the risk of severe bleeding.[103,104] The usual dose is 5 or 6 units of random donor platelets or 1 plateletpheresis unit, which is equivalent to 5 or 6 random donors. In theory, 1 unit of platelets can raise the count by 50,000 to 70,000/μL, but often this response is blunted by concurrent illness or bleeding. In patients who appear to have a poor response, the platelet count can be checked 15 minutes after platelet infusion. No rise or a minimal rise (<20,000/μL) in the platelet count is suggestive of platelet refractoriness, while a good 15-minute response but poor 24-hour count is more suggestive of consumption—fever, sepsis, drug, or splenomegaly—and not refractoriness.

BLEEDING IN THE PLATELET-REFRACTORY PATIENT

Many patients with cancer, particularly hematologic cancers, become resistant to transfused platelets. Bleeding in patients who are refractory to platelet transfusion presents a difficult clinical problem (**Table 5**).[105] If patients are demonstrated to have HLA antibodies, one can transfuse HLA-matched platelets.[106] Unfortunately, matched platelet transfusions may not be available and do not work in 20% to 70% of these patients. One can perform platelet cross-matching to find compatible units for these patients, but this may not always be successful. Use of antifibrinolytic agents such as ε-aminocaproic acid or tranexamic acid may decrease the incidence of bleeding. Platelet drips consisting of infusing either 1 platelet concentrate per hour or 1 plateletpheresis unit every 6 hours may be given as a continuous infusion. For life-threatening bleeding, rVIIa may be of use. For platelet-refractory patients with arterial bleeding the use of angiographic delivery of platelets has been reported to be successful in stopping bleeding.[107]

CONCLUSION

Bleeding in cancer patients can occur for many reasons, but knowing the underlying diagnosis and previous (if any treatments) plus obtaining basic laboratory tests can allow for effective management for most patients.

BOARD REVIEW QUESTIONS

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