Benign Hematological Diseases in Cancer Patients

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Abstract

Cancer patients frequently develop hematological problems that require direct management. Understanding their pathophysiology provides one with important clinical insight that directs appropriate therapeutic interventions.

Keywords

Thrombocytopenia · Neutropenia · Anemia · Coagulopathy · Thrombosis · Hypercoagulability

Introduction

The semantic distinction between benign and malignant hematology focuses a problem and its diagnostic and therapeutic interventions, but it is lost when one attends to critically ill cancer patients. These patients inevitably have several interconnected disease processes inseparable from their primary oncological diagnosis, treatment programs, and comorbidities. The goal for effective management is to identify and rank the various pathophysiological processes operating over time. The benign hematologist does this from the perspective of changes expressed by the blood, changes which often provide unique and clinically important insights. Such insights can be essential for optimizing outcomes in critically ill cancer patients.

Anemia

Anemia in the cancer patient is frequently multifactorial in etiology, often secondary to the physiologic derangements brought about by systemic cancer and a side effect of cancer treatment. As with anemias in general, etiologies of anemia in cancer patients can be grouped into three broad categories: conditions of hypoproliferation, destruction, and blood loss.

The estimated prevalence of anemia in cancer patients varies widely in published reports, depending on the definition of anemia and stage of disease. The majority of late-stage cancer patients are anemic, and patients with hematologic malignancies are more likely to be anemic [11]. The incidence of anemia is as high as 90% in patients receiving chemotherapy [23]. Clinical manifestations of anemia ultimately depend on the degree of impairment of tissue oxygenation, and tissue oxygenation is the driver of erythropoiesis through synthesis of erythropoietin in the kidney. In cancer patients, increase in circulating inflammatory cytokines such as TNF-alpha promotes anemia through multiple mechanisms, including decreased production of erythropoietin coupled with inadequate response of the bone marrow to erythropoietin. This is compounded by chemotherapeutic agents, some of which act directly on pathways of erythropoiesis [13]. The most common symptom of anemia is fatigue, which is especially prevalent among cancer patients. Life-threatening anemia in the critical care setting presents with evidence of tissue hypoxia and organ damage, manifesting as shortness of breath, cognitive impairment, headache, palpitations, and dizziness; severe anemia in critical illness may present with loss of consciousness, pulmonary edema, or heart failure.

Hypoproliferative Anemia

The cancer patient may be receiving myelosuppressive treatments (cytotoxic chemotherapy, radiation therapy) or have replacement of the bone marrow by cancer. Malignancy frequently produces a chronic inflammatory state and with this anemia of chronic inflammation, in which cytokine-mediated changes disrupt normal erythropoiesis. Difficulties maintaining adequate nutrition in the course of cancer treatment may lead to

deficiencies in essential micronutrients required for hematopoiesis, including iron, vitamin B12, and folic acid.

Anemia Due to Red Blood Cell Destruction

In cancer patients destruction may be mechanical, drug-induced, autoimmune, or associated with microangiopathic hemolysis. Drug-induced hemolytic anemia is seen with numerous medications used in the course of cancer treatment, including multiple antibiotics, chemotherapeutics, and antiemetics [6]. Particularly in hematologic malignancies, immune dysregulation can promote red cell destruction through the development of warm autoantibodies, cold agglutinins, pure red cell aplasia, and hemophagocytic lymphohistiocytosis [13]. Cancer-associated thrombotic microangiopathies (see below), manifesting as microangiopathic hemolytic anemia and thrombocytopenia, are linked to several drugs used in cancer treatment and develop in up to a quarter of hematopoietic stem cell transplant recipients [12].

Anemia from Blood Loss

Hemorrhage may occur as a consequence of thrombocytopenia or coagulopathy, both of which may be secondary to the malignancy or its treatment. Acquired hemophilia, though rare, may present with bleeding sufficient to be life-threatening in cancer patients, particularly those with hematologic malignancies [4]. Certain cancers (e.g., gastric, hepatic, ovarian, retroperitoneal tumors) can cause significant internal bleeding through direct invasion of vasculature.

Diagnosing Anemia

Anemia is frequently defined as hemoglobin <12 g/dL for adult women and <14 g/dL for adult men; any cancer patient with a hemoglobin less than 11 g/dL warrants further workup per the NCCN guidelines [19]. Evaluation should be driven by suspected etiology and tempered by acuity and severity. A comprehensive history, with special attention to the type of cancer and treatments received, guides laboratory workup, which should always include a peripheral blood smear. When hypoproliferative anemia is suspected, iron studies, vitamin B12, and folic acid levels should be sent, and bone marrow biopsy is considered. Autoimmune hemolytic anemias are characterized by positive antiglobulin (Coombs) testing, elevated LDH and reticulocyte count, decreased haptoglobin, and microspherocytosis on the peripheral blood smear. Microangiopathic hemolytic anemias show schistocytes and red cell fragmentation and are distinguishable from disseminated intravascular coagulation (DIC) by the absence of alterations in coagulation studies [20]. Bleeding sufficient to cause symptomatic anemia in the critical care setting is usually evident on history, though identification of the bleeding source may require advanced imaging or endoscopy.

Treating Anemia

Treatment of anemia in the critical care setting almost always involves transfusion. Current guidelines from the NCCN recommend transfusing symptomatic patients with a goal of achieving tissue oxygenation and hemodynamic stability. Asymptomatic patients should be transfused for a hemoglobin less than 7 g/dL [19]. The use of erythropoiesis-stimulating agents (ESAs) such as erythropoietin or darbepoetin in cancer patients remains controversial, with some data suggesting it may be harmful [15]. ESAs can be considered in patients who refuse blood transfusion or who have moderate to severe chronic kidney disease [19].

Thrombocytopenia

Thrombocytopenia results from bone marrow underproduction, immune destruction, consumption, and splenic-mediated sequestration. Each of these processes can affect cancer patients, and identifying the mechanism of thrombocytopenia will determine prognosis and treatment.

Chemotherapy-Induced Thrombocytopenia

Chemotherapy that inhibits cell proliferation causes myelosuppression accompanied by underproduction thrombocytopenia. While there are many mechanisms by which cancer therapies affect the bone marrow (Table 1), for most myelosuppressive agents, platelet production is shut down for a few days, resulting in a nadir that reflects the normal 7 day half-life of circulating platelets and develops about 7–10 days after treatment. Carboplatin, temozolomide, and the nitrosourea compounds affect platelet production for a longer period of time, leading to thrombocytopenia that may last for 3 weeks or longer.

Platelet transfusions are the standard treatment for chemotherapy-induced thrombocytopenia, and their indications are solidly established: asymptomatic patients with no signs of impaired hemostasis can receive prophylactic platelet transfusions when the count falls below 10,000/μl; those who have mild bleeding when the count falls below 20,000/μl; those with major bleeding or who are perioperative when the count falls below 50,000/μl; and those with spinal or brain trauma, hemorrhage, or surgery when the count falls below 100,000/μl. Recent guidelines provide platelet count parameters for various invasive procedures commonly used in the ICU setting [21]. While thrombopoietic agents are FDA approved for treating thrombocytopenia from immune thrombocytopenia, hepatitis C, and idiopathic aplastic anemia, their usefulness in chemotherapy-induced thrombocytopenia remains uncertain.

Non-chemotherapy-Induced Thrombocytopenia

Various drug classes are associated with thrombocytopenia: heparins, quinine/quinidine, platelet glycoprotein IIb-IIIa inhibitors (abciximab, tirofiban, eptifibatide), gold, penicillamine, linezolid, vancomycin, sulfonamides, rifampin, cephalosporins, carbamazepine, phenytoin, valproic acid, diazepam, H2 antagonists, acetaminophen, diclofenac, naproxen, ibuprofen, hydrochlorothiazide, and chlorothiazide. Mechanisms and kinetics of thrombocytopenia are pleiotropic, but it usually develops after about 1 week of continuous therapy and resolves 7–14 days after discontinuation [2].

Immune Thrombocytopenia

Two forms of immune thrombocytopenia are encountered in oncologic critical care: alloimmune thrombocytopenia and autoimmune thrombocytopenia. Alloimmune thrombocytopenia is due to HLA-A and HLA-B incompatibility between a donor and the platelet transfusion recipient. It is minimized by using platelet transfusions judiciously, providing ABO compatible platelets and leukodepleting platelets pretransfusion. Alloimmunization will still develop in about 15% of patients with acute leukemia and recipients of stem cell transplantation and is one mechanism by which patients become refractory to platelet transfusions. Measuring anti-HLA antibodies in platelet refractory patients and/or obtaining HLA-A/B compatible platelets is sometimes useful, although anti-HLA antibodies are ephemeral and results that are obtained just a day or two after measurement may already be clinically irrelevant [7]. Autoimmune thrombocytopenia (ITP) may arise de novo or be associated with lymphoproliferative or rheumatological diseases. It is a diagnosis of exclusion, results in mucocutaneous bleeding symptoms and signs in about one-third of patients, and first-line treatment is with corticosteroids (and high-dose intravenous immunoglobulin when there is overt hemorrhage) when the platelet count falls to $<$30,000/μl [17].

DIC

Disseminated intravascular coagulation is always secondary to an underlying problem, most commonly sepsis. It is defined by laboratory parameters (coagulopathy, thrombocytopenia and microangiopathic hemolytic anemia), with most patients suffering mild to moderate bleeding and, rarely, microvascular thromboses. Treatment for

Table 1 Myelosuppressive effects of cancer treatments

Drug class	Alkylating agent	Platinum compounds	Antimetabolites	Topoisomerase II inhibitors	Antimicrotubule agents	Immunomodulators	Proteasome inhibitors	VEGF inhibitors	EGFR inhibitors
Mechanism of action	Inhibit DNA synthesis through covalent binding of an alkyl group to DNA	Inhibition of DNA repair and synthesis through DNA cross-linking	Inhibition of DNA synthesis through competition with purines and pyrimidines and through DNA damage	Inhibition of topoisomerase II, an enzyme responsible for DNA unwinding	Disruption of normal cell division by stabilization of microtubules	Stimulates cellular immune system, inhibits inflammatory cytokines, inhibits angiogenesis	Alters intracellular function by preventing degradation of pro-apoptotic factors and other essential proteins	Inhibition of angiogenesis	Block the extracellular ligand-binding domain or the intracellular tyrosine kinase domain to inhibit the epidermal growth factor receptor, thus disrupting cell proliferation
Neutropenia	Common	Common	Dose-dependent – common with high-dose cytarabine, uncommon with typical doses of 5-fluorouracil	Common	Common	Common	Common	Uncommon when used as a single agent	Uncommon when used as a single agent
Thrombocytopenia	Common	Common	As above	Common	Common	Common	Common	As above	As above
Anemia	Common	Common	As above	Common	Common	Common	Common	As above	As above
Miscellaneous	Agranulocytosis observed when used in combination with other cytotoxic chemotherapy drugs					Myelosuppression is correlated with worsening renal function; cause thromboses			

(*continued*)

Table 1 (continued)

Drug class	BCR-Abl inhibitors	c-KIT inhibitors	PDGFR inhibitors	Ras/Raf/MEK/MAP kinase pathway inhibitors	PI3-K inhibitors	BTK inhibitors	ALK inhibitors	MET inhibitors	RET inhibitors	mTOR inhibitors
Mechanism of action	Deactivation of the ABL tyrosine kinase, shutting down the constitutive auto-phosphorylation that results in abnormal cell proliferation	Blocks the receptor tyrosine kinase c-KIT, which is mutated in several cancers, resulting in uncontrolled cell proliferation	Blocks activity of two tyrosine kinase receptors (PDGFR-α and PDGFR-β), which promote tumor cell growth	Mutations in this pathway result in activation of RAF kinases, causing uncontrolled cell growth; thus, targets of this pathway inhibit cancer cell proliferation	Blocks one or more PI3-kinase enzymes, which are part of the **PI3K**/AKT/mTOR pathway, an important signaling pathway for many cellular functions such as growth control, metabolism and translation	Blocks Bruton's tyrosine kinase, which controls the B-cell antigen receptor on mature B cells and allows for their persistence and uncontrolled proliferation	Anaplastic lymphoma kinase is a tyrosine kinase that is constitutively activated in ALK-mutated NSCLC, resulting in uncontrolled cell proliferation	Blocks the increased signaling in the MET pathway seen in some cancers, which results in tumor cell proliferation and survival	Blocks the activity of RET rearrangement mutations, which result in fusion proteins that promote uncontrolled cell growth, primarily in adenocarci-nomas of the lung	Activation of mTORC1 downstream of PI3K and AKT increases the production of proteins, lipids, and nucleotides while downregulating autophagy, which supports cell survival, growth, and proliferation federation
Neutropenia	Common	Common	Common	Uncommon	Uncommon	Common	Common	Common	Common	Uncommon
Thrombocytopenia	Common	Common	Common	Uncommon	Uncommon	Common	Common	Common	Common	Uncommon
Anemia	Common	Common	Common	Uncommon	Uncommon	Common	Common	Common	Common	Common
Miscellaneous							Causes lymphopenia			

Drug class	Cell cycle inhibitors	PARP inhibitors	Aurora kinase inhibitors	Immune checkpoint inhibitors	Procarbazine	Asparaginase	Hypomethylating agents	Histone deacetylase inhibitors	Rituximab
Mechanism of action	Slow or stop the normal cell cycle progression through various mechanisms	Block activity of the enzyme poly ADP ribose polymerase, which prevents cancer cells from repairing DNA damage	Blocks activity of aurora kinases, which are enzymes involved in various aspects of mitosis and are overexpressed in various cancers	Blocks the binding of PD-1 to PD-L1, resulting in improved ability of T cells to kill tumor cells	Reduction in DNA synthesis through covalent binding of an alkyl group	Breaks down asparagine, which is used by cancer cells in multiple processes in cell replication	Decrease the amount of DNA methylation, disrupting patterns of excess DNA methylation affecting tumor suppressor genes in some cancers	Histone deacetylases act on histone tails to promote chromatin compaction and transcriptional repression; inhibition of this process induces cell cycle arrest and apoptosis in cancer cells	Monoclonal antibody to CD-20, expressed in B-cell malignancies, induces killing of CD20+ cells through multiple mechanisms
Neutropenia	Common	Uncommon when used as a single agent but can compound myelosuppressive effect when used with cytotoxic therapy	Common	Uncommon	Common	Uncommon	Common	Common	Uncommon
Thrombocytopenia	Common	As above	Common	Uncommon	Common	Uncommon	Common	Common	Uncommon
Anemia	Common	As above	Common	Uncommon	Common	Uncommon	Common	Common	Uncommon
Miscellaneous	Cause lymphopenia	Cause lymphopenia		Associated with immune-mediated cytopenias	Immune hemolytic anemia has been reported	Associated with antithrombin deficiency and hypofibrinogenemia			Lymphopenia is a concern; late-onset neutropenia has been reported

hemorrhagic DIC is blood product replacement with FFP to restore coagulation factors, cryoprecipitate to restore fibrinogen, and platelet transfusions to achieve a count of 30,000–50,000/μl. In patients with thrombotic DIC, low-dose infused unfractionated heparin has improved and even resolved microvascular ischemia [14].

Thrombotic Microangiopathies

Cancer-associated thrombotic microangiopathies (TMAs) are a group of disorders identified mainly by descriptive clinical characteristics always involving the presence of circulating schistocytes associated with intravascular hemolysis (elevated LDH and indirect bilirubin), anemia, and, when the bone marrow is healthy, elevated reticulocytes. Anemia and thrombocytopenia are the principle clinical manifestations, but there may also be end-organ dysfunction from microvascular thrombosis, particularly in the kidneys. Cancer-associated TMAs are distinguished from disseminated intravascular coagulation by normal coagulation studies and D-dimer levels.

The molecular pathogenesis of cancer-associated TMAs is barely understood, and ignorance about pathophysiological mechanisms is coupled to inadequate diagnostic measures and a paucity of effective evidence-based clinical therapeutics. Most of the approaches utilized derive from those used to manage patients with two of the well-characterized TMAs: de novo thrombotic thrombocytopenic purpura from acquired ADAMTS-13 deficiency and hereditary complement-mediated TMA (also referred to as familial atypical hemolytic uremic syndrome due to a deficiency in complement regulatory protein). Such approaches are rarely effective.

There are rare but predictable clinical associations between TMA and some malignancies and their treatments [16]. These may provide general clarity about pathogenesis, and their recognition often provides a useful management strategy for patients with microangiopathic hemolytic anemia and thrombocytopenia, particularly when the TMA is due to a drug that can be replaced with an effective alternative agent. TMA is most likely to develop in patients with gastric > breast > prostate > lung > lymphoma > unknown primary cancer. Paraneoplastic TMA almost always develops in patents with bone marrow metastases and can involve a DIC-like coagulation picture. It rarely involves any end-organ injury and appears to be treatable only with effective chemotherapy. Several antineoplastic drugs have been repeatedly associated with TMA, including mitomycin C, gemcitabine, interferons, pentostatin, sunitinib, bevacizumab, oxaliplatin, and docetaxel. TMA is also predictably associated with drugs used routinely in the management of stem cell transplant: the calcineurin inhibitors cyclosporine and tacrolimus and the mTOR inhibitors sirolimus and everolimus. End-organ injury, should it occur, mainly involves the kidneys and is reversible after stopping the drug.

TMAs in cancer patients are a heterogeneous group of diagnoses, almost all of which have common clinical correlates and a final common pathway of microvascular thromboses that threaten or injure the kidneys. Dissecting established pathophysiological elements of de novo TTP (VWF and ADAMTS-13) and aHUS (complement over activity), putative pathophysiological elements of chemotherapy and post-SCT TMA (direct endothelial toxicity and cytokine "storms"), and vague pathophysiological elements of paraneoplastic TMA (myelophthisis and coagulation system activation) may someday allow clinicians to establish diagnostic criteria and treatments that are based on a hierarchy of pathophysiological factors driving each individual case.

Hypersplenism

Splenic sequestration typically results in mild neutropenia and thrombocytopenia [18]. It is usually associated with splenomegaly caused by infectious diseases; hematological malignancies; solid tumor metastasis; portal hypertension from liver diseases (including metastasis); portal venous thrombosis from surgery, regional cancers, and myeloproliferative neoplasms; and sequestration of red blood cells in immune and nonimmune hemolytic anemias. Hypersplenic cytopenias are rarely clinically significant and rarely require treatment, although

thrombocytopenia and neutropenia can confound plans to administer chemotherapy at optimal dose and schedule. In these cases, splenic artery embolization or splenectomy can restore counts capable of supporting optimal cytotoxic chemotherapy.

Neutropenia

Neutropenia is a common problem in the oncology critical care unit, developing as a complication of the malignancy and/or its treatment. Neutropenia is a risk factor for severe bacterial infections, including sepsis, when the absolute neutrophil count falls below 1000/μl, but risk increases geometrically as the count falls further to 500/μl and below. The management of neutropenic fever is presented in a separate chapter in this volume.

Congenital Neutropenia

Severe congenital neutropenia is a life-threatening condition identified in infancy requiring life-long treatment with a myeloid growth factor (such as G-CSF) [25]. On the other end of the spectrum is benign constitutional or ethnic neutropenia, which is relatively common in African Americans [8] and poses no clinical threat except when it unnecessarily confounds conventional neutrophil parameters used to dose-reduce or delay therapy [9].

Chemotherapy-Induced Neutropenia

Chemotherapy-induced neutropenia develops predictably with all cytotoxic chemotherapy (Table 1). The onset of chemotherapy-induced neutropenia is earlier than chemotherapy-induced thrombocytopenia (the life span of circulating neutrophils is about 24 h while platelets circulate for at least a week), but its duration is comparable. There is a dose response and an accumulating toxicity that often directs specific colony-stimulating factor (CSF) interventions, as described in recent clinical practice guidelines [22]. Of note, CSF support is not part of the conventional management of febrile neutropenic patients.

Non-chemotherapy Drug-Related Neutropenia

Table 2 shows that a variety of drugs cause isolated neutropenia and agranulocytosis [1]. The magnitude of clinical impact is dependent on the degree of neutropenia. Fever, mouth sores, gingivitis, skin infections, and throat infections signal the presence of a clinically significant neutropenia and direct the use of CSF as well as appropriate antibiotics. Like non-chemotherapy drug-induced thrombocytopenia, these neutropenias are of

Table 2 Non-chemotherapy drugs causing neutropenia

Anti-inflammatory	Acetaminophen, aspirin, diclofenac, ibuprofen, indomethacin, naproxen, sulfasalazine, diflunisal, dipyrone, phenylbutazone, piroxicam, sulindac, fenoprofen, mefenamic acid, gold, levamisole, infliximab, penicillamine
Anticonvulsant	Carbamazepine, phenytoin, valproic acid, ethosuximide, lamotrigine
Antibiotics	Beta-lactams, cephalosporins, sulfonamides, macrolides, chloramphenicol, vancomycin, flucytosine, quinine, isoniazid, nitrofurantoin, abacavir, indinavir, acyclovir, ganciclovir, terbinafine, amphotericin
Antipsychotics and antidepressants	Clozapine, phenothiazines, risperidone, olanzapine, fluoxetine, amitriptyline, citalopram, imipramine, desipramine, clomipramine, doxepin, amoxapine
Antithyroid	Propylthiouracil, carbimazole, methimazole
Cardiovascular	Procainamide, quinidine, amiodarone, disopyramide, aprindine, clopidogrel, ramipril, spironolactone, captopril, metolazone, furosemide, thiazides, digoxin, propranolol, acetazolamide
Gastrointestinal	Cimetidine, metoclopramide, ranitidine, famotidine, mesalazine, omeprazole
Miscellaneous	Deferiprone, allopurinol, promethazine, aminoglutethimide, levamisole, rituximab

uncertain mechanisms but usually develop after beginning a new medication and resolve within 2 weeks of stopping the drug.

Diseases Associated with Neutropenia

In the ICU setting, sepsis is easy to recognize as the cause of neutropenia, and one must recognize that systemic viral infections usually cause neutropenia. Patients with rheumatological conditions may suffer autoimmune neutropenia or Felty's syndrome. Splenomegaly, whether from Felty's syndrome or another cause, may result in mild neutropenia usually coupled to thrombocytopenia. Neutropenia is an obvious manifestation of primary hematological malignancies or metastatic cancer affecting the bone marrow, and it is always important to consider vitamin B12, folic acid, and copper deficiencies as underlying neutropenia. These conditions, as well as those associated with myelophthisis or a primary bone marrow malignancy, inevitably cause qualitative and quantitative changes in all blood cells that are easily recognized by examining the CBC and blood smear.

Coagulopathy

Coagulopathy affects up to 10% of cancer patients with solid tumor malignancies and a larger number of patients with hematologic malignancies. The pathophysiology of coagulopathy is complex in cancer patients. As tumor cells interact with the circulatory system through the elaboration of procoagulant factors, angiogenesis, vascular invasion, and metastasis, they disturb the balance of the coagulation system, which can disrupt normal hemostasis *and* promote thrombosis [5]. Both solid tumors and hematological malignancies are associated with a hypercoagulable state, while life-threatening hemorrhagic disorders directly attributable to hypocoagulation are a hallmark of hematologic malignancies.

Coagulopathy in Cancer Patients

Hematologic malignancies cause disruption of the normal physiology of blood. Thrombocytopenia, discussed in detail above, is a common feature of malignancy involving the bone marrow, and it is a frequent side effect of myelosuppressive chemotherapy. Acute promyelocytic leukemia (APL) is associated with a complex coagulopathy resembling DIC; bleeding is frequently a presenting symptom and is thought to be the number one cause of early death in APL [26]. It is minimized by treating patients with all-trans retinoic acid before cytoablative chemotherapy; this differentiates the APL blasts into neutrophils, eliminating procoagulant primary granules and surface receptors on the APL cells that assemble the fibrinolytic apparatus.

Both solid tumors and blood cancers lead to the development of neutralizing autoantibodies against coagulation factors. These acquired inhibitors mostly target factor VIII, causing dramatic and often intractable bleeding requiring intensive hemostatic support and immune suppression for weeks to months before recovery can be expected [4]. In contrast, Trousseau's syndrome is chronic cancer-associated DIC that causes consumptive coagulopathy, thrombocytopenia, and microvascular thrombosis [24]. It is most common in mucin-secreting adenocarcinomas and cancers that metastasize to the intravascular compartment, such as melanoma. Microvascular ischemia will often improve using low doses of infused unfractionated heparin.

Other Causes of Coagulopathy

Anticoagulant therapy is common among cancer patients and should be ruled out as the first step in the evaluation of bleeding. Liver disease resulting in decreased synthesis of coagulation factors can be seen in cancer patients as a result of intrinsic liver disease, hepatic metastases, and injury from chemotherapy. It manifests itself as elevated PT and aPTT that correct with 1:1 mixing and can be distinguished from vitamin K deficiency by decreased factor V and VII levels. Hepatic coagulopathy requires treatment with coagulation factor replacement using fresh frozen plasma, and infusing cryoprecipitate when the fibrinogen level falls below 100 mg/dL. Vitamin K deficiency from poor nutrition and/or oral antibiotics is frequently encountered in cancer patients. It is identified by an elevated

PT that corrects with 1:1 mix, proven by decreased factor VII with a normal factor V level, and is reversed by the administration of oral or parenteral vitamin K.

Hyperfibrinolysis sometimes emerges in patients with large tumor burden urothelial cancers, which express a urokinase-like plasminogen activator protein leading to systemic fibrinolysis. This is identified by low levels of fibrinogen associated with very high circulating D-dimers without any abnormality of the PT and aPTT. It is proven by thromboelastography or by measuring clot lysis time in urea and treated with fibrinogen replacement and an antifibrinolytic agent.

Congenital coagulation disorders, when mild, may evade detection until a cancer diagnosis demands testing and treatment; von Willebrand disease should be considered in patients with unexplained bleeding, particularly if there is a personal or family history of easy bruising or bleeding.

Management of Coagulopathy

Management of coagulopathy should be directed at the underlying cause and, in many situations (e.g., acquired hemophilia), requires expert guidance by a hematologist (Table 3). The first principle of management of coagulopathy in the critical care setting is to treat bleeding (or bleeding risk, when surgical procedures are planned) rather than laboratory values [10]. The use of platelet transfusions for thrombocytopenia is discussed above. Bleeding secondary to deficiencies in coagulation factors may be managed with transfusion of blood products (fresh frozen plasma, cryoprecipitate, four-factor prothrombin complex concentrate, factor infusions); establishment of institutional guidelines for the use of blood products can be helpful to guide this practice. Vitamin K deficiency is common among critical care patients, and its replacement may be indicated. Support with antifibrinolytic therapies (aminocaproic acid, tranexamic acid) is commonly used for treatment and prophylaxis of bleeding in patients with refractory thrombocytopenia.

Table 3 Management of common bleeding disorders

Defect	Interventions
Underproduction thrombocytopenia	Platelet transfusion
Immune thrombocytopenia	Corticosteroids (+ high-dose IVIG if bleeding)
Refractory thrombocytopenia	Antifibrinolytic therapy (aminocaproic acid or tranexamic acid)
DIC or hepatic coagulopathy	Coagulation factor replacement with FFP; fibrinogen replacement with cryoprecipitate
Vitamin K deficiency	Vitamin K
Hypofibrinogenemia	Cryoprecipitate
Hyperfibrinolysis	Cryoprecipitate + antifibrinolytic therapy
Warfarin toxicity	Unactivated 4 factor prothrombin complex (*KCentra*) or FFP + vitamin K
Unfractionated or low molecular weight heparin toxicity	Protamine (+ recombinant-activated factor VII [rFVIIa] when there is intracranial bleeding)
Dabigatran	Idarucizumab for major bleeding and activated prothrombin complex (FEIBA) for clinically significant nonmajor bleeding
Rivaroxaban, apixaban, edoxaban, betrixaban	Unactivated 4 factor prothrombin complex (andexanet alfa is antidote for major bleeding)
Fondaparinux	rFVIIa for major bleeding
Acquired factor VIII inhibitor	Corticosteroids, cyclophosphamide and rFVIIa or activated prothrombin complex
Von Willebrand disease	Von Willebrand factor replacement
Hemophilia	Factor VIII, IX, or XI replacement

Hypercoagulability

Hypercoagulability is a state of increased risk for thrombosis [3]. The risk is often presented as a relative risk, hazard ratio, or annual incidence. Increased risk may relate to venous, arterial, and microvascular thrombosis, and thrombosis risk is measured (and usually different) for both initial

and recurrent events. Hypercoagulability is also designated "thrombophilia," and there are inherited and acquired hypercoagulable states. Most patients with thrombosis are found to have predispositions and triggers, and the challenge is to identify and rank them with an eye toward optimizing therapy to prevent recurrent thrombosis safely. In most cases of thrombosis, "hypercoagulability" is considered to be a predisposing factor separate from other risk factors for atherothrombotic disease (such as smoking and hypercholesterolemia) and venous thrombosis (such as hormonal therapy and immobility). Hypercoagulability is also typically considered to represent a pathological condition (so that pregnancy, while associated with increased risk of venous thromboembolism [VTE], is usually not considered a hypercoagulable state). A hypercoagulable state should be suspected when a patient has any of the following:

- Idiopathic thrombosis at any age
- Family history of venous thromboembolism
- Thrombosis at unusual sites such as cerebral, hepatic, mesenteric, renal, or portal veins
- Recurrent unprovoked/unexplained thromboses
- Recurrent unexplained fetal loss
- Warfarin-induced skin necrosis
- Purpura fulminans
- Recurrent superficial thrombophlebitis

Mechanisms of Hypercoagulability

The inherited thrombophilias are caused by increased activity of procoagulant proteins (factor V and prothrombin) or decreased activity of natural anticoagulant proteins (antithrombin, protein C, and protein S). These proteins are all part of the soluble coagulation system, which operates to generate insoluble fibrin. Fibrin deposition resulting in thrombosis can only develop in low flow vascular systems. Accordingly, the inherited hypercoagulable states result only in venous thrombosis. These thromboses can occur in any venous compartment but are typically DVT (of legs > arms), PE, splanchnic vein thrombosis, and cerebral vein thrombosis. The acquired thrombophilias lead to widespread vascular perturbation and are associated with both VTE and arterial thromboses such as coronary, cerebral, and peripheral arterial ischemia and infarction. Arterial thromboses are rarely de novo, and hypercoagulability-induced arterial thromboses are most frequent in patients who are known to suffer atherothrombotic arterial occlusive disease.

Inherited Hypercoagulability

The common inherited hypercoagulable states are *factor V Leiden* and *prothrombin G20210A*, which are due to mutations in the genes for factor V and prothrombin. *Factor V Leiden* is a point mutation in factor V that renders factor V resistant to breakdown by activated protein C (R506Q), and *prothrombin G20210A* is a mutation in the noncoding region of the prothrombin gene that results in increased protein synthesis (prothrombin levels of 110–120%). Less common inherited hypercoagulable states are due to deficiencies of the natural anticoagulant proteins *antithrombin*, *protein C*, and *protein S*. Mutations in the folate metabolizing enzyme *MTHFR* (methylenetetrahydrofolate reductase) leading to elevated blood homocysteine levels are sometimes mistakenly designated an inherited hypercoagulable state.

Acquired Hypercoagulability

The antiphospholipid syndrome is the most important cause of acquired hypercoagulability. It develops de novo or secondary to lymphoproliferative or rheumatological conditions. Other acquired hypercoagulable states are heparin-induced thrombocytopenia, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, and cancer. The prevalence of cancer-associated VTE varies with the type of malignancy and its treatment. It is associated with an average relative risk of a first VTE of about 6 with absolute 6-month incidence of recurrence – on anticoagulation – of nearly 10%.

Occult Cancer and Hypercoagulability

Two issues to consider are occult malignancy and occult myeloproliferative neoplasm (MPN). At least 5% of patients with idiopathic VTE will have a cancer diagnosed within the next 12 months. There is no standard US approach to evaluating these patients, but in the UK all unprovoked VTEs trigger an evaluation that includes complete history and examination, CBC, LFTs, calcium, urinalysis, and CXR, and we recommend appropriate imaging to evaluate any abnormality, particularly to look for occult digestive, gynecological, or thoracic malignancies. One must also look for MPN in patients with splanchnic vein thromboses, as at least 10% of them will have undiagnosed MPN; over half of those with hepatic vein thrombosis (Budd-Chiari syndrome) will be diagnosed with JAK2 V617F (+) MPN or paroxysmal nocturnal hemoglobinuria (PNH). Women with recurrent fetal loss and signs of a blood disorder (hemolysis or cytopenias) should be tested for PNH.

Testing for Hypercoagulability

Hypercoagulability should be tested for in any individual with a single unprovoked venous thromboembolic event. In the absence of a family history, testing is limited to the antiphospholipid syndrome (lupus anticoagulant, antiphospholipid antibodies, and anti-β2 glycoprotein-1 antibodies). In the presence of a history of a first-degree relative with VTE, testing for the five inherited thrombophilias should be undertaken. Any patient with a personal *and* family history of venous thrombosis should be tested for an inherited hypercoagulable state. No testing of any type should be done for a patient with provoked VTE, unless there is a family history. Asymptomatic blood relatives of patients with inherited thrombophilia may be screened in order to provide counseling about VTE symptoms and signs and in order to optimize prophylaxis in high-risk situations. There is no reason to test for any of the inherited thrombophilias in patients with myocardial infarction, stroke, or peripheral vascular disease. The antiphospholipid syndrome is often tested for in young patients with myocardial infarction or stroke without arterial occlusive disease or any obvious cardiac source of arterial thromboembolism, but evidence for this is ambiguous. Less ambiguous are data that one must test for the antiphospholipid syndrome in every woman who has suffered recurrent first trimester or a single second or third trimester miscarriage.

Testing for factor V Leiden, prothrombin G210210A, antiphospholipid antibodies, and anti-β 2 glycoprotein-1 antibodies can be done at any time. Testing for antithrombin, protein C, protein S, and the lupus anticoagulant should be done at least 3 weeks off anticoagulation, with repeat testing after 3 months. Note that the direct factor Xa inhibiting anticoagulants (rivaroxaban, apixaban, and edoxaban), give a false (+) lupus anticoagulant screen.

Conclusion

The non-malignant hematologic conditions reviewed in this chapter, while traditionally labeled as "benign," can frequently have dire implications in the critically ill oncology patient.

References

1. Andersohn F, Konzen C, Garbe E. Systemic review: agranulocytosis induced by nonchemotherapy drugs. Ann Intern Med. 2007;146:657–65.
2. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. N Engl J Med. 2007;357:580–7.
3. Connors JM. Thrombophilia testing and venous thrombosis. N Engl J Med. 2017;377:1177–87.
4. Escobar MA. Bleeding in the patient with a malignancy: is it an acquired factor VIII inhibitor? Cancer. 2012;118:312–20. https://doi.org/10.1002/cncr.26304.
5. Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects. J Thromb Haemost. 2012;11:223–33.
6. Garratty G, Arndt PA. An update on drug-induced immune hemolytic anemia. Immunohematology. 2007;23:105–19.
7. Hod E, Schwartz J. Platelet transfusion refractoriness. Br J Haematol. 2008;142:348–60.
8. Hsieh MM, Everhart JE, Byrd-Holt DD, Tisdale JF, Rodgers GP. Prevalence of neutropenia in the US population: age, sex, smoking status and ethnic differences. Ann Intern Med. 2007;146:486–92.

9. Hsieh MM, Tisdale JF, Rodgers GP. Neutrophil count in African Americans: lowering the target cutoff to initiate or resume chemotherapy? J Clin Oncol. 2010;28:1633–7.
10. Hunt BJ. Bleeding and coagulopathies in critical care. N Engl J Med. 2014;370:847–59.
11. Knight K, Wade S, Balducci L (2004) Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med. https://doi.org/10.1016/j.amjmed.2003.12.008.
12. Laskin B, Goebel J, Davies S, Jodele S. Small vessels, big trouble in the kidneys and beyond: hematopoietic stem cell transplantation–associated thrombotic microangiopathy. Blood. 2011;118:1452–62. https://doi.org/10.1182/blood-2011-02-321315.
13. Lebovic D. (2018) Anemia in Malignancy. In: Provenzano R., Lerma E., Szczech L. (eds) Management of Anemia. Springer, New York, NY.
14. Levi M, Scully M. How I treat disseminated intravascular coagulation. Blood. 2018;131:845–54.
15. Leyland-Jones B, Bondarenko I, Nemsadze G, et al. A randomized, open-label, multicenter, phase III study of Epoetin alfa versus best standard of care in anemic patients with metastatic breast cancer receiving standard chemotherapy. J Clin Oncol. 2016;34:1197–207. https://doi.org/10.1200/JCO.2015.63.5649.
16. Morton JM, George JN. Microangiopathic hemolytic anemia and thrombocytopenia in patients with cancer. J Oncol Pract. 2016;12:522–30.
17. Neunert CE. Management of newly diagnosed immune thrombocytopenia: can we change outcomes? Blood Adv. 2017;1:2295–301.
18. Pozo AL, Godfrey EM, Bowles KM. Splenomegaly: investigation, diagnosis and management. Blood Rev. 2009;23:105–11.
19. Rodgers GM et al. Cancer- and chemotherapy-induced anemia. NCCN Clinical Practice Guidelines in Oncology Version 2.2018 – 11/21/2017. 2017.
20. Sanford RA, Kroll MH. Cancer-associated thrombosis. In: Kantarjian HM, Wolff RA, editors. The MD Anderson manual of medical oncology. 3rd ed. New York: McGraw-Hill; 2016.
21. Schiffer CA, Bohlke K, Delaney M, et al. Platelet transfusion for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2018;36:283–99.
22. Smith TJ, Bohlke K, Armitage JO. Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology clinical practice guideline update. J Oncol Pract. 2015;11:511–3.
23. Tas F, Eralp Y, Basaran M, et al. Anemia in oncology practice: relation to diseases and their therapies. Am J Clin Oncol. 2002;25:371–9.
24. Varki A. Trousseau's syndrome: multiple definitions and multiple mechanisms. Blood. 2007;110:1723–9.
25. Gibson C, Berliner N. How we evaluate and treat neutropenia in adults. Blood. 2014;124(8):1251–8. https://doi.org/10.1182/blood-2014-02-482612.
26. Mantha S et al. Determinants of fatal bleeding during induction therapy for acute promyelocytic leukemia in the ATRA era. Blood. 2017;129(13):1763–1767. https://doi.org/10.1182/blood-2016-10-747170.