Bleeding and Thrombosis

FAST FACTS

- **Description**: Bleeding can result from a reduction in platelets, an alteration in clotting factors, a paraneoplastic syndrome, infection, hepatic problems, or a combination of these factors. Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism (PE).
- **Incidence**: Bleeding can occur with any type of cancer but especially in patients with advanced cancer and those with hematologic malignancies. Annual incidence of VTE is five times greater in patients with cancer than in the general population. Newer therapies including thalidomide, lenalidomide, and bevacizumab have higher rates of VTE.
- **Clinical Manifestations**: Signs of bleeding: petechiae, ecchymoses, bruising, epistaxis, hemoptysis, hematemeses, melena, hematuria, vaginal bleeding. Signs of DVT: unilateral swelling of extremity, edema, warmth, localized pain, vein dilation, limb color changes, pyrexia. Signs of PE: dyspnea, pleuritic pain, tachypnea, apprehension, tachycardia.
- **Evaluation/Diagnostic Tests**: Bleeding: complete blood count (especially hemoglobin and platelet levels), coagulation tests. DVT: D-dimer, venous duplex ultrasound, computed tomography scans. PE: computed tomography pulmonary angiogram, ventilation/perfusion scans.
- **Treatment Modalities**: Bleeding: transfusions, vitamin K therapy, vasopressive hormones, mechanical measures. VTE: Prophylaxis with low-molecular-weight heparin (LMWH), unfractionated heparin, factor Xa inhibitors, and mechanical prophylaxis for at-risk nonambulatory hospitalized patients. Therapy with LMWH or vitamin K antagonists may continue indefinitely for patients with active cancer.
- **Nursing Management**: Recognition of early signs and symptoms of bleeding or coagulation is key in the nurse’s assessment. Bleeding precautions are implemented for at-risk patients. Nursing measures are instituted to prevent VTE in hospitalized patients and those at risk. VTE is the most preventable cause of death in hospitalized patients.
- **Outcome**: Patients with cancer are at high risk for bleeding and VTE. Early recognition and initiation of appropriate treatment are crucial to patient outcome. Those at risk for VTE are considered for pharmacologic prophylaxis, balancing the risk of VTE with the increased risk of bleeding.

Introduction

Abnormalities in hemostasis, including bleeding and thrombosis, are common complications in patients with cancer and can greatly affect morbidity and mortality (Gouin-Thibault, Achkar, & Samama, 2001). Several factors can contribute to the etiology of bleeding and thrombosis, including the disease process and the use of treatment modalities that may affect bleeding or coagulation.
These include surgical procedures, chemotherapy, biotherapy, radiation therapy, central venous catheters, supportive care with colony-stimulating factors, and newer anticoagulants (DeSancho & Rand, 2001; Prandoni, Falanga, & Piccioli, 2005). Several tumor-related or treatment-related factors can increase the risk for bleeding by disrupting normal hemostatic mechanisms. Among them are a reduction in the quantity or functional quality of platelets, an alteration in clotting factors, the development of a paraneoplastic syndrome, or a combination of factors (Damron et al., 2009). These disturbances can have a direct effect on patient mortality and morbidity and present complex challenges when caring for patients with cancer. Because bleeding poses dire consequences for patients, it is imperative that prevention of bleeding be included in the management plan. In order to increase survival rates, rapid recognition, assessment of the precipitating factors, and knowledge of the treatment of bleeding are necessary. Ongoing bleeding can affect patients’ quality of life by causing fatigue and weakness and can progress to an issue of safety if life-threatening hemorrhage occurs (Tipton, 2009). Being able to recognize signs of bleeding can dramatically improve patients’ quality of life and increase their potential for survival. Oncology nurses, both in outpatient and inpatient settings, play a key role in preventing and managing major bleeding events and should be knowledgeable about evidence-based interventions for this side effect (Damron et al., 2009).

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is the most preventable cause of death in hospitalized or recently hospitalized patients (Hacking, Hellewell, & Sadler, 2005). PE causes more death in the United States than AIDS and breast cancer combined, with approximately 10% of all hospital deaths attributed to PE (Meissner et al., 2007). Untreated proximal leg DVT progresses to PE in about 50% of cases (Morrison, 2006). VTE is the second leading cause of death in both hospitalized and ambulatory patients with cancer (Khorana, 2009; Khorana, Francis, Culakova, Kuderer, & Lyman, 2007b). Patients with cancer have a much higher risk of either developing a new DVT or having DVT recur compared to patients who do not have cancer (Alikhan et al., 2004; Kuderer, Ortel, & Francis, 2009; Zaki, Wright, & Cushman, 2004). The highest risk for DVT recurrence is in the first few months following cancer diagnosis, but the risk persists for many years after the initial DVT (Blom, Doggen, Osanto, & Rosendaal, 2005; Khorana, 2009).

The appearance of VTE may indicate the presence of malignancy. Bura et al. (2004) studied 103 patients with DVT and found that 25% were known to have cancer at admission, and a new cancer was diagnosed in 26% of those without known cancer at admission. In addition, 62% of the patients with known cancers and 70% of the patients with new cancers already had metastatic disease. The odds of cancer in this study were nearly five times higher for patients with idiopathic thrombosis than for those with secondary thrombosis. VTE adversely affects quality of life. In a study by Kahn et al. (2005), the effects of VTE were measured using the SF-36® physical component summary (PCS)
and mental component summary scores. The mean PCS scores among patients who had VTE were lower than those in the general population at baseline, one month, and four months. The scores in these patients were also lower at one month than the scores in patients who had arthritis or chronic lung disease.

Because treatment for VTE requires hospitalization, management of DVT adds considerably to healthcare costs and resources (Elting et al., 2004). Complications of VTE can extend the hospital stay by 7–11 days, adding a mean of $1,784 (2002 USD) per day to hospitalization costs (Elting et al., 2004). In the same retrospective study of medical records from 529 patients with cancer, the mean hospitalization cost for DVT was $20,065 (2002 USD) compared with a cost of $7,712–$10,804 per episode in a general medical population with VTE (Dobesh, 2009; Elting et al., 2004).

Bleeding has been shown to complicate the survival rate in patients undergoing blood and hematopoietic stem cell transplantation. In one study, 23% of patients receiving human leukocyte antigen (HLA)-identical stem cells and 45% of patients receiving non-HLA-identical stem cells experienced hemorrhage (Bacigalupo, 2003).

### Incidence

Bleeding, in general, can occur with any type of cancer, and there are no specific incidence rates for this complication. However, bleeding does occur more frequently in individuals with hematologic cancers because these cancers affect the bone marrow, often resulting in thrombocytopenia. Therefore, the incidence and severity of bleeding in patients with acute leukemia are greater than in patients who have solid tumors. Bleeding occurs in up to 10% of patients with acute promyelocytic leukemia, and patients can consequently suffer fatal hemorrhagic complications (Rodriguez & Gobel, 2011).

Solid tumors are more prone to having hemostatic abnormalities, especially the mucin-producing adenocarcinomas such as those of the lung, breast, stomach, pancreas, and prostate (Avances et al., 2003). However, these solid tumors are thought to be more commonly associated with disseminated intravascular coagulation (DIC), which will be discussed more thoroughly in Chapter 3. Certain malignancies have a higher incidence of bleeding, including large head and neck carcinomas, large centrally located lung cancers, acute myeloid leukemia, and chronic myeloid leukemia (Rodriguez & Gobel, 2011). Up to 90% of patients with acute promyelocytic leukemia will develop a hemorrhagic complication (DeSancho & Rand, 2001). Of these, 10% will suffer a fatal hemorrhagic complication (Rodriguez & Gobel, 2011).

Thrombotic complications occur more frequently in the setting of malignancy. Patients with cancer have an estimated fivefold higher annual incidence of VTE than the general population. The incidence in the general population is approximately 1 in 1,000, whereas in patients with cancer, the annual incidence increases to 1 in 200 (Khorana, 2007). In a retrospective study of more than 66,000 hos-
hospitalized neutropenic adults with cancer, Khorana et al. (2006) found that 5.4% of patients developed VTE over eight years of the study. However, the reported rates of VTE in patients with cancer are believed to be underestimated given that autopsy rates of VTE can be as high as 50% compared with clinical rates of 4%–20% (Gomes & Deitcher, 2003; Khorana, 2007). In an analysis of more than 66,000 patients with cancer hospitalized at 120 U.S. academic medical centers, 5.4% developed VTE per hospitalization, increasing by 36% from 1995 to 2002 (Khorana et al., 2006). Similarly, an analysis of the National Hospital Discharge Survey found that the incidence of VTE increased nearly twofold from 1980 to 1999 (Stein et al., 2006). The reasons for this increased incidence in patients with cancer are uncertain. However, vascular toxicity, particularly thromboembolism, is a specific adverse effect of antiangiogenic drugs. Newer cancer regimens that include thalidomide, lenalidomide, or bevacizumab have reported very high rates of VTE (Kabbinavar et al., 2003; Khorana, Francis, Culakova, Kuderer, & Lyman, 2007a; Kuenen et al., 2003; Nalluri, Chu, Keresztes, Zhu, & Wu, 2008; Shah, Llson, & Kelsen, 2005; Zangari et al., 2004).

**Risk Factors**

**Bleeding**

Several factors increase the risk of bleeding in patients with cancer. Antineoplastic therapies increase the risk for bleeding by damaging normal tissues. Radiation therapy and steroid treatment can cause blood vessels to become very fragile and more prone to injury, while chemotherapy and radiation can cause myelosuppression, including thrombocytopenia, which increases the risk of bleeding (Friend & Pruett, 2004). Infection, DIC, liver disease, and medication-induced platelet dysfunction also may cause bleeding in patients with cancer (Kwaan & Vicuna, 2007).

Because of the critical role that platelets play in hemostasis and thrombosis, the platelet count is considered to be the single most significant factor for predicting bleeding in a patient with cancer (Rodriguez & Gobel, 2011). The first reported association between thrombocytopenia and bleeding risk occurred in 1962, when it was demonstrated that hemorrhage rarely occurred in patients with acute leukemia when the platelet count remained higher than 20,000 cells/mm³ (Gaydos, Frieric, & Mantel, 1962). Platelet function can be affected by numerous drugs, in particular aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Kwaan & Vicuna, 2007). Both drug types can drastically reduce platelet aggregation, with the effects of aspirin lasting up to four days after ingestion. A newer class of NSAIDs, the COX-2 inhibitors, has a lesser effect on platelets than other NSAIDs and may be an option for patients with cancer (Friend & Pruett, 2004).

Antibiotic use can also contribute to bleeding risk by impairing platelet function. Carbencillin, ticarcillin, and penicillins impair the aggregation of
platelets and prolong the bleeding time (Friend & Pruett, 2004). This platelet dysfunction is usually reached three to five days after the beginning of antibiotic therapy and continues for three to four days after the therapy is completed. Other medications that suppress platelet function include phenothiazines, tricyclic antidepressants, heparins, cimetidine, thiazide diuretics, and estrogen. In addition, corticosteroids affect the gastric mucosa and impair wound healing. This results in the skin becoming thin and fragile and more susceptible to bleeding (Friend & Pruett, 2004).

Tumor growth can lead to bleeding through invasion into the surrounding structures and blood vessels, as well as the bone marrow. Leukemias and lymphomas are the most common types of cancers associated with bone marrow invasion. In these diseases, the malignant cells crowd out the normal cells in the marrow, leading to thrombocytopenia, anemia, and neutropenia. Tumors also can erode and enter mucous membranes and cause bleeding by local tissue disruption. Tumors that are close to large blood vessels put individuals at risk for a massive hemorrhage. Other risk factors for bleeding among patients with cancer include leukostasis, leukoencephalitis, and liver metastases in patients with solid tumors (Friend & Pruett, 2004; Kwaan & Vicuna, 2007).

Infection, mainly sepsis, increases the risk of bleeding in several situations. DIC, a possible complication of sepsis, can result in a fatal bleeding event (Kwaan & Vicuna, 2007). Periods of febrile neutropenia are associated with the greatest bleeding risk. An infection within the gastrointestinal (GI) or genitourinary tract can irritate or ulcerate the mucosal linings, thereby increasing the risk for bleeding events. Viruses can cause myelosuppression or thrombocytopenia, and fungal infections, especially in the lungs, can cause fatal hemorrhage (Friend & Pruett, 2004). Fever has been known to increase the risk of bleeding and also potentially affects a patient’s response to a platelet transfusion (Kwaan & Vicuna, 2007). Vitamin K is needed for proper coagulation. Malnutrition can lead to an increased risk of bleeding because of a deficiency in vitamin K, which can develop as a direct result of a dietary deficiency, biliary obstruction, malabsorption syndromes, liver disease, and anticoagulation therapy (Friend & Pruett, 2004).

The presence of uremia is another risk factor for bleeding. Bleeding in uremic patients most commonly manifests in the mucocutaneous areas and puncture sites as ecchymosis, purpura, and epistaxis, GI and genitourinary bleeding, and subdural hematomas (Friend & Pruett, 2004).

**Venous Thromboembolism**

The presence of cancer is a well-established independent risk factor for development of VTE, with almost one-fifth of all new VTE events being associated with active cancer (Alikhan et al., 2004). Epidemiologic studies have shown the risk for VTE to be significantly higher in patients with cancer. In a population-based case-control study, the overall risk for VTE was sevenfold higher in patients with cancer than in those without malignancy (Blom et al.,
In addition to the independent variable of cancer, risk for development of VTE can be divided into patient-, disease-, and treatment-related factors (see Table 1-1).

**Patient-Related Risk Factors**

Patient-related factors for VTE include age, sex, ethnicity, comorbid conditions, and prothrombotic mutations. Khorana et al. (2006) showed that patients with cancer of advanced age (older than 65 years) and women were at higher risk for developing VTE. Ethnicity has been reported to play a role in thrombotic risk in patients with breast cancer, whereby African Americans were shown to be at higher risk and Asians/Pacific Islanders at lower risk for VTE (Chew, Wun, Harvey, Zhou, & White, 2006). Obese patients, as well as those

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with a known infection, renal disease, pulmonary disease, or arterial thromboembolism, and those with a prior history of VTE are at higher risk for developing VTE (Alcalay et al., 2006; Khorana et al., 2006; Kroger et al., 2006). More recent studies have investigated common genetic mutations that promote thrombosis as a source of risk for developing VTE. Mutations in factor V Leiden and prothrombin G20210A have been identified as increasing the risk for VTE (Eroğlu, Kurtman, Ula, Çam, & Akar, 2005; Eroğlu, Ulu, Çam, Kurtman, & Akar, 2007; Kennedy et al., 2005).

**Disease-Related Risk Factors**

Disease-related factors include the site, stage, and duration of the cancer. Sites of cancer with the highest rates of VTE include the pancreas (8.1%), kidneys (5.6%), ovaries (5.6%), lungs (5.1%), and stomach (4.9%) (Blom et al., 2005; Chew et al., 2006; Khorana et al., 2007a; Stein et al., 2006). The risk of VTE in patients with hematologic malignancies was also high, especially for patients with non-Hodgkin lymphoma and leukemia, who accounted for more than one-third of all patients with venous events (Khorana et al., 2006). The highest rates of VTE were seen in patients with non-Hodgkin lymphoma (4.8%) and Hodgkin lymphoma (4.6%) (Khorana et al., 2006). The risk of developing VTE varies over the natural history of the cancer, with the highest risks occurring during hospitalization and after development of metastasis (Chew et al., 2006; Rao, Francis, & Khorana, 2007). A large study of patients with non-Hodgkin lymphoma revealed that thrombosis was present at the time of diagnosis in 37% of the patients, during the first cycle of chemotherapy in 22%, and within the first three cycles of chemotherapy in 82% (Komrokji et al., 2006). Incidence of VTE is highest during the first year of follow-up and decreases significantly over time for all types and stages of cancer with the exception of localized pancreatic cancer (Alcalay et al., 2006; Chew et al., 2006).

**Treatment-Related Risk Factors**

Treatment-related factors include pharmacologic and nonpharmacologic therapies. Many therapies including surgery, chemotherapy, and biotherapy, and supportive treatments place patients at greater risk for developing VTE. Hospitalized patients, as well as those who have recently undergone surgery, are at higher risk as well (Agnelli et al., 2006; Andtbacka et al., 2006; Behranwala & Williamson, 2009; Bergqvist, 2007; Khorana et al., 2006; Kroger et al., 2006; Osborne, Wakefield, & Henke, 2008). Chemotherapy increases the risk of developing VTE, with studies indicating a 6.5-fold increase in risk (Khorana & Rao, 2007; Lyman et al., 2007). Studies of some of the newer cancer regimens, especially those including antiangiogenesis therapies such as thalidomide, lenalidomide, and bevacizumab, have reported very high rates of VTE (Kabbinavar et al., 2003; Kuenen et al., 2003; Lyman et al., 2007; Shah et al., 2005).
The use of thalidomide in conjunction with chemotherapy or dexamethasone in patients with multiple myeloma increases the risk of VTE (Lyman et al., 2007). In a meta-analysis of 17 randomized controlled trials, Gray, Chu, Wu, and Lin (2008) studied the use of thalidomide in 3,977 patients who had multiple myeloma and a variety of solid tumors. The overall incidence of VTE was 11.7%; patients treated with thalidomide demonstrated double the risk of VTE compared with controls. This risk was especially high in patients with multiple myeloma, with 15% of those patients developing VTE—triple the risk compared with control patients not receiving thalidomide.

The risks of DVT with the use of lenalidomide, a structural analog of thalidomide, have not proved to be significant (Yang et al., 2009). The use of lenalidomide in conjunction with erythropoiesis-stimulating agents (ESAs) in patients with myelodysplastic syndromes (MDS) did show an increased risk of VTE. However, lenalidomide without the use of ESAs demonstrated no increased risk (Yang et al., 2009).

Bevacizumab, a monoclonal antibody with antiangiogenic properties, has increased survival rates when used in combination with chemotherapy in patients with colorectal or nonsquamous cell lung cancers. However, findings related to bevacizumab and VTE are controversial. Data from randomized controlled trials evaluated combination treatment with bevacizumab and chemotherapy versus chemotherapy alone in 1,745 patients with colorectal, breast, or nonsquamous cell lung cancer. A twofold increase in arterial thromboembolic events was shown, but no increase in risk of VTE was evident (Scappaticci et al., 2007). This is in contrast to a more recent systematic review and meta-analysis by Nalluri et al. (2008). These authors evaluated 7,956 patients with a variety of advanced solid tumors from 15 randomized controlled trials. Results indicated that bevacizumab was associated with an increased risk of VTE compared with controls.

Some supportive therapies can increase a patient’s risk of developing VTE. The use of ESAs, including epoetin alfa and darbepoetin alfa, has been associated with DVT. A meta-analysis of 35 studies reported that treatment with epoetin or darbepoetin increased the risk of DVT by 67% compared with patients not receiving these agents (Bohlius et al., 2006). The use of red blood cell transfusions can also increase the risk of developing DVT. Khorana et al. (2008) reported that 7.2% of patients receiving transfusions developed VTE and 5.2% developed arterial thromboembolism compared to 3.7% and 3.0%, respectively, of patients who did not receive transfusions.

**Pathophysiology**

**Bleeding**

Normal control of bleeding (hemostasis) is maintained through a finely regulated balance between clot formation (coagulation) and clot dissolution.
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The presence of malignancy disrupts this essential balance and can lead to bleeding through several different mechanisms, including alterations in platelet count and function, activation of the coagulation cascade, disruption in vascular integrity, and the effects of antineoplastic therapies. Patients with cancer often have more than one of these conditions occurring concurrently, putting them at increased risk for bleeding (Rodriguez & Gobel, 2011).

Bleeding can be caused by local and systemic factors, alone or in combination. Local anatomic causes of bleeding include tumor extension and invasion of blood vessels, whereas systemic causes include bone marrow invasion by tumor cells, bone marrow suppression from chemotherapy or radiation, and the development of DIC (see Chapter 3). Other systemic factors contributing to bleeding risk include liver failure, medications such as anticoagulants, aspirin, and NSAIDs, and concomitant disease such as liver cirrhosis (Gagnon, Mancini, Pereira, & Bruera, 1998). See Table 1-2 for an overview of the etiology of bleeding.

The Role of Platelets

Platelets play a crucial role in the process of hemostasis. Platelets are not true cells, but rather fragments of megakaryocytes, giant cells within the bone marrow that are integral to the production of platelets. When fragmented, a megakaryocyte can release more than 1,000 platelets. The major hormone involved in this process is thrombopoietin. In the event of an injury or cut that breaks the endothelial layer of a blood vessel, platelets function as first

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responders to form a clot that seals the injury site and inhibits blood loss (George, 2011). Disorders of platelet function and platelet abnormalities can affect the clotting process and put an individual at risk for severe and possibly fatal bleeding.

Thrombocytopenia, a reduction in the number of circulating platelets, is the platelet abnormality most frequently associated with cancer. Several factors are linked with the development of thrombocytopenia, including reduced platelet production, a change in platelet distribution, increased platelet destruction, vascular dilution of platelets, platelet consumption as seen in DIC, and some drug therapies (Avvisati, Tirindelli, & Annibali, 2003).

Decreased platelet production can occur secondary to direct invasion of the bone marrow by tumor cells or from the myelosuppressive effects of chemotherapy or radiation therapy on the marrow. When the bone marrow is occupied by a large burden of tumor cells that overwhelms the normal elements, the resulting thrombocytopenia reflects an overall pancytopenia in which all cell lines are reduced. The occurrence and severity of treatment-associated thrombocytopenia depend on the type of chemotherapy drugs used, their dosage, and the time elapsed between treatments. With radiation therapy, the development of thrombocytopenia depends on the amount of bone marrow encompassed in the treatment fields. The development of thrombocytopenia may be a dose-limiting factor in delivering these treatments and can lead to a bleeding event (Kwaan & Vicuna, 2007; Rodriguez & Gobel, 2011).

Thrombocytopenia may arise indirectly in patients with cancer whose spleens have enlarged as a result of infection, inflammation, autoimmune disorder, or neoplasm within the spleen. Spleenic pooling of platelets has been identified as a cause of thrombocytopenia, with approximately one-third of transfused platelets being removed from circulation and sequestered in the spleen (Takamatsu et al., 2007). Spleenic enlargement may be seen with metastasis to the spleen from cancers of the lung, breast, colon, prostate, and stomach, as well as lymphomas. If the spleen is not enlarged, it is unlikely that existing thrombocytopenia is being caused by splenic trapping of platelets (Rodriguez & Gobel, 2011).

Thrombocytopenia may develop when platelet destruction is increased, a feature of idiopathic thrombocytopenic purpura, an autoimmune disorder in which autoantibodies are formed against the individual’s own platelets. Immature platelets accumulate in the bone marrow while the number of circulating mature platelets diminishes. This presentation is most often found in patients with lymphomas and may precede clinical diagnosis (Rodriguez & Gobel, 2011).

When thrombocytopenia persists despite treatment with platelet transfusions, the patient may be refractory to the platelets. Reports cite a 15%–25% incidence of refractoriness to platelet transfusions in hematology/oncology patients when using leukocyte-reduced blood products and even higher rates prior to the use of leukoreduction (Hod & Schwartz, 2008; Slichter et al., 2005). Two categories of platelet refractoriness exist: nonimmune and immune.
Nonimmune

Causes of nonimmune refractoriness include sepsis, fever, bleeding, splenomegaly, and DIC. Fever, one of the most frequently cited causes, most likely is not an independent factor but rather is associated with underlying infection or sepsis. DIC results in an increased rate of platelet consumption, which can result in refractoriness. Splenomegaly is a well-established cause of poor response to platelet transfusion. Normally, about one-third of a person’s platelets are sequestered in the spleen, which is in equilibrium to the circulating platelet pool. In extreme splenomegaly, up to 90% of the platelets can be sequestered (Wang et al., 2012).

Immune

Refractoriness to platelet transfusion caused by an immune response is known as alloimmunization and has the greatest potential for prevention and management. Some platelet antigens, such as HLA, are shared by other blood cells and tissues, with HLA-A and HLA-B antigens most likely responsible for alloimmunization. To counteract this effect, leukoreduced platelets can be used to decrease the potential for alloimmunization. Another antigen, human platelet antigen, is specific to platelets only. Some studies have shown that patients who developed red blood cell antibodies were more likely to also have HLA antibodies (Buetens et al., 2006).

Clotting Factor Deficiencies

Clotting factor deficiencies can contribute to bleeding risk and may occur with certain cancers. Patients with solid tumors, hematologic cancers, myeloproliferative disorders, macroglobulinemia, and lymphoproliferative disorders may acquire von Willebrand disease, in which factor VIII procoagulant activity is diminished or absent. Patients who present with this syndrome usually have increased bruising, mucosal bleeding, and GI hemorrhage (Rodriguez & Gobel, 2011).

Clotting factors I, II, V, VII, IX, and X are synthesized in the liver; therefore, conditions that compromise liver function, such as infection, chemotherapy, tumor invasion, and even surgery, can contribute to prolonged bleeding times. The liver is also the site where fibrin degradation products and activated clotting factors are cleared from the circulation. Thus, impairment of liver function disturbs normal coagulation (Rodriguez & Gobel, 2011). In addition, patients with cancer who undergo extensive surgical procedures may receive large amounts of fresh frozen plasma and may become prone to increased bleeding, as fresh frozen plasma is deficient in factors V and VIII (Rodriguez & Gobel, 2011). Deficiency of clotting factor III may be seen with acute leukemias and MDS and is associated with impaired procoagulant activities and abnormal platelet function caused by alterations in platelet size, shape, and aggregation responses (Rodriguez & Gobel, 2011).
Coagulation

Many factors contribute to the general prothrombotic state present in patients with cancer. In 1856, Virchow described three mechanisms that are integral to thrombosis formation. Commonly referred to as the Virchow triad, these mechanisms include blood flow, vessel integrity, and blood components (Kwaan & Vicuna, 2007) (see Figure 1-1). Later, Trousseau (1865) elaborated on the cellular components within blood and was the first to discuss the relationship between malignancy and coagulation (Kwaan & Vicuna, 2007).

Blood Flow

The first mechanism involved in coagulation is normal blood flow. The normal fluidity, or viscosity, of blood depends upon a balance between the plasma fluid in the blood and the cellular components. Changes in one or both of these elements may occur in patients with cancer, resulting in atypical blood flow and an increased prothrombotic risk. Under normal physiologic conditions, whole blood viscosity is a function of the plasma viscosity, the hematocrit, and red cell aggregation. When plasma viscosity increases, as may happen with high levels of plasma proteins or high fibrinogen levels, hyperviscos-
ity of whole blood occurs, contributing to thrombotic risk. The brain, myocardium, lungs, and kidneys are especially vulnerable to the development of microthrombi, which most often manifest as headache, visual changes, chest pain, and dyspnea (Kwaan & Vicuna, 2007).

The role of fibrinogen levels in relation to blood viscosity was demonstrated in one study using a therapeutic defibrination agent. Results showed that when fibrinogen levels were reduced to 5 mg/dl, blood viscosity was greatly reduced but returned to normal when the fibrinogen level was restored to 270 mg/dl, which is within the normal range. This effect on blood viscosity is significant given that patients with cancer, especially renal cell and ovarian cancers, frequently have high fibrinogen levels (Koh, Khalil, Lim, Llancheran, & Choolani, 2006; Ogata et al., 2006). Comorbid conditions such as infection, which is common in cancer, also can increase fibrinogen levels. In addition, it has long been recognized that high fibrinogen levels increase the risk for cardiovascular events.

Immunoglobulins, which are plasma proteins, also affect viscosity and blood flow. Immunoglobulins can cause red cell dysplasia, in which the ability of normal red blood cells to change their shape to flow through small spaces, especially in the microvasculature, is reduced and red cell aggregation can result. In the presence of high levels of plasma proteins, red cells begin to stack together or create long chains that can be seen in peripheral blood smears. This is known as rouleaux formation (Kwaan & Vicuna, 2007). Plasma viscosity is increased proportionately to the quantity and size of the plasma protein. Hyperviscosity is most common with the proteins immunoglobulin M and immunoglobulin A (Kwaan & Vicuna, 2007).

The cellular components of blood also have an effect on the blood’s ability to flow freely. The consequences of high hematocrit levels have been studied with conflicting results. In earlier studies it was believed that a high hematocrit was a thrombotic risk factor. This led to the recommendation of maintaining a hematocrit level less than 45% (Schafer, 2006). However, more recent studies have showed that hematocrit measures taken at the same time as thrombotic events were not associated with increased risk (Di Nisio et al., 2007).

Hyperleukocytosis, a high white blood cell count, is a common finding in acute and chronic leukemias. This can lead to leukostasis, a condition in which white blood cell plugs develop within the microcirculation of the central nervous and respiratory systems. This is most commonly found in acute myeloid leukemia and acute promyelocytic leukemia because the myeloblasts are larger and less able to change shape than normal neutrophils (Kwaan & Vicuna, 2007). Leukostasis is less commonly seen in the lymphoid leukemias because the cells are smaller and more deformable and have a lower adherence to the vasculature (Kwaan & Vicuna, 2007).

Elevated platelet levels have been identified in the pathogenesis of VTE. In a study of 3,003 outpatients with cancer, 58 VTE events were detected. In those patients with prechemotherapy platelet counts greater than 350,000/microliter, the incidence of VTE was significantly increased (Khorana, Francis, Culakova, & Lyman, 2005).
External compression resulting from tumor growth can impede blood flow. An example of this would be in superior vena cava syndrome, which can cause thrombosis. However, it has been shown that superior vena cava thrombosis is more often caused by central venous catheters rather than extrinsic compression. In a retrospective analysis of more than 34,000 hospitalized patients, only six had superior vena cava thrombosis, primarily attributed to central venous catheters (Otten, Stein, Patel, Mustafa, & Silbergleit, 2003). Thrombosis caused by compression has also been seen in bulky lymphadenopathy that occurs in lymphoma. This is often caused by the lymph nodes in close proximity to vasculature. In a retrospective review of 211 patients with lymphoma, of which 27 had VTE, 11 were associated with enlarged lymph nodes causing external pressure on blood vessels (Komrokji et al., 2006).

Immobilation associated with surgery or hospitalization can result in decreased and impaired blood flow. Patients who undergo oncologic surgery have twice the risk of thrombosis because of the underlying cancer and the resulting immobility. Several studies have shown this increased risk following colorectal, lung, breast, and gynecologic cancer surgeries (Agnelli et al., 2006; Andtbacka et al., 2006; Bergqvist, 2006; Le Treut et al., 2006; Martino et al., 2006).

**Vessel Integrity**

Vascular integrity is breached when the tumor directly invades or extends into the endothelial cell wall. Tumor cells produce prothrombotic factors that can be a major constituent of the resulting clot, especially when the site of invasion is adjacent to the primary tumor. This is most often seen in the portal vein with hepatocellular carcinoma and in the inferior vena cava and right atrium with renal cell carcinoma (Kwaan & Vicuna, 2007).

Cytokines play an important role in the formation of thrombi and compromise of vascular integrity. The close proximity of tumor cells, endothelial cells, and stromal cells provide the opportunity for cytokine-mediated interactions. Proinflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor-beta, are produced by tumor cells. Once released, these cytokines stimulate tissue factor (TF) expression on monocytes, thereby causing the monocyte to bind to the platelet. At the same time, they down-regulate anticoagulant factors, including thrombomodulin and plasminogen activator inhibitor-1 (PAI), creating an environment for thrombus formation (Kuderer et al., 2009).

**Blood Components**

Tumor cells produce several factors that can disrupt coagulation and fibrinolytic systems and lead to a prothrombotic state in cancer. These factors include TF, cancer procoagulant, and PAI. TF is a transmembrane glycoprotein receptor that initiates the coagulation cascade. When activated, TF assembles several complexes that lead to thrombin production. TF can also be induced
by proinflammatory cytokines as previously discussed or by vascular trauma. Both plasma TF antigen and leukocyte TF have been found to be elevated in patients with DVT (Kamikura et al., 2005).

Cancer procoagulant (CP) is a cysteine protease procoagulant derived from tumor cells. CP works by directly activating the clotting factor, factor X. CP has been found in the cells of both solid tumors and hematologic cancers. A correlation is suspected between CP and fibrinogen in patients with adenocarcinoma. In acute promyelocytic leukemia, CP is thought to be downregulated by all-trans-retinoic acid treatment. CP may induce platelet activation via a mechanism similar to thrombin; however, more studies need to be done to clearly understand the role of CP in thrombosis (Kwaan & Vicuna, 2007).

Plasminogen activator is a component of the fibrinolytic system that is expressed in tumor cells. Elevated levels of PAI have been linked to the increased risk of VTE in patients with cancer, as well as those without cancer (Lisman, de Groot, Meijers, & Rosendaal, 2005).

It has been suggested that the components of the clotting cascade and the vascular factors associated with them play an important role in tumor progression, invasion, angiogenesis, and metastatic formations (Kuderer et al., 2009; Palumbo, Mullins, & Degen, 2008; Palumbo et al., 2005). In addition, some interesting in vitro studies have indicated that anticoagulants, especially low-molecular-weight heparin (LMWH), have antineoplastic properties that can interfere with metastasis formation (Ludwig et al., 2004; Stevenson, Choi, & Varki, 2005).

**Clinical Manifestations**

**Bleeding**

Bleeding is manifested in several ways in patients with cancer. Signs of bleeding without visible hemorrhage include petechiae, ecchymoses, and bruising. This type of bleeding may often be overlooked because it is not thought of as active bleeding and manifests in covert signs. Overt signs of bleeding include epistaxis, hemoptysis, hematemesis, melena, hematuria, vaginal bleeding, and bleeding around wounds and vascular access devices (Damron et al., 2009). Bleeding can begin slowly and present as oozing but can progress into an acute hemorrhagic event. Even the smallest amount of bleeding can eventually lead to absolute anemia, which is defined as a reduction in the number or volume of circulating red blood cells.

Anemia is not a disease but rather a symptom of another disorder. If bleeding is present in patients with cancer, anemia will most likely develop. Patients can present with symptoms of anemia including fatigue, pallor, dizziness, irritability, weakness, chest pain, shortness of breath, decreased body temperature, and numbness in the hands and feet. Hypotension and tachycardia may be present. Many symptoms of anemia are nonspecific, and
a drastic reduction in the red blood cell count may occur before absolute anemia is diagnosed. Because there is not an easy or practical way of measuring this, the more typical measurement used is accepted anemia, which is a reduction in one or more of the major red blood cell measurements including the hemoglobin concentrate, hematocrit, and red blood cell count (Damron et al., 2009).

More than 400 types of anemia exist, which are classified by either etiology or morphology (Schrier, 2010). Etiologic classifications focus on the cause of the anemia. Etiologically, anemia can be caused by a decreased production of red blood cells as seen with bone marrow suppression, by increased red blood cell destruction as seen with hemolysis or blood loss, or by lack of hormones such as erythropoietin to stimulate production of red blood cells. Morphologic classifications focus on changes in the erythrocyte itself, such as the color, shape, or size.

Morphologically, anemias are classified as microcytic, macrocytic, or normocytic. In microcytic anemias, the red blood cell is smaller in size than normal with a mean corpuscular volume (MCV) of less than 80 femtoliters (fL) and is usually accompanied by a decrease in hemoglobin content. The most common types of microcytic anemias are thalassemia, iron-deficiency anemia, and anemia of chronic disease (Schrier, 2010). In macrocytic anemias, the red blood cell is larger than normal, with an MCV of greater than 100 fL with accompanying abnormal nucleic acid production and abnormal red blood cell maturation. Macrocytic anemias most commonly occur with MDS and acute leukemia (Schrier, 2010). Normocytic anemias have a normal-sized red blood cell with an MCV of 80–100 fL. Normocytic anemia is seen with endocrine disorders, acute blood loss, myelosuppression, and early iron-deficiency anemia (Schrier, 2010).

Several organ systems are sensitive to the effects of bleeding and anemia. In the renal system, the kidneys respond to decreased blood flow by releasing renin, an enzyme that participates in maintaining blood pressure by stimulating salt and water retention, which in turn can lead to edema (Schrier, 2010). The decreased oxygen levels that accompany chronic anemia can cause hair to become thin and gray. In the nervous system, anemia affects nerve fibers by causing degeneration of myelin, leading to loss of nerve fibers. Effects of anemia on the GI system are manifested as abdominal pain, nausea, and vomiting. The skin loses elasticity in response to the decreased oxygenation associated with anemia. Table 1-3 provides an overview of the effects of bleeding on selected organ systems. It is important for the nurse to instruct patients about the signs and symptoms of anemia and the need for immediate follow-up with their physicians.

**Thrombosis**

Although there are classic clinical manifestations of VTE, 50% of the cases of DVT and up to 75% of cases of PE have no initial observable symptoms.
Chapter 1. Bleeding and Thrombosis

(Morrison, 2006). PE should be considered in patients who present with the three most frequent signs: dyspnea, pleuritic chest pain, and tachypnea. Less frequent signs are cough, hemoptysis, fever, syncope, diaphoresis, nonpleuritic chest pain, apprehension, rales, wheezing, hypotension, tachycardia, cyanosis, or pleural rub. Massive PE can present with hemodynamic instability or cardiac arrest (Borgstrom et al., 2012). Recent unilateral swelling and pain above or below the knee without explanatory bone or joint trauma is suspicious for DVT (Borgstrom et al., 2012). Other signs of DVT include edema, warmth, localized pain, dilatation of veins, color changes of limb, and pyrexia. Edema may be caused from decreased venous return as a result of the embolism or capillary damage causing leakage of intravascular fluid into the surrounding tissue, distal to the thrombosis site (Morrison, 2006). When the affected limb is warm, it is most likely due to localized venous congestion and accumulation of tissue metabolites. Pain can be experienced in the calf muscle during dorsiflexion of the foot. This is known as a Homans’ sign. However, one study found that only 37% of patients with VTE had a positive Homans’ sign and 21% of patients without VTE also had positive Homans’ sign (McCaffrey & Blum, 2009). Dilation of a vein causing a palpable cord over a superficial vein is a result of systemic and peripheral venous circulatory stasis (Borgstrom et al., 2012). Initially, pallor of the skin might be the only indicator of DVT. In other cases, erythema occurs immediately over the DVT site as a result of superficial thrombophlebitis. Pyrexia, a systemic increase in body temperature, can be caused by the accumulation of tissue metabolites at the site of the thrombosis.

Upper-extremity DVT (UEDVT) has become an increasingly recognized source of morbidity and mortality and represents an estimated 1%–4% of all cases of DVT (Kearon et al., 2008). UEDVT can occur in the subclavian, axillary, or brachial veins with clinical symptoms consisting of edema, arm pain or discoloration, or the development of collateral veins involving the affected arm, neck, or chest wall. An acute complication of UEDVT is PE, which
can occur in up to 33% of patients, only half of whom may be symptomatic (Burns & McLaren, 2008).

Patient Assessment

Assessment should begin with a thorough history. A complete bleeding history, including signs of bleeding such as easy bruising, nosebleeds, gingival bleeding, petechiae, and a change in the color of stools or urine should be obtained. The patient should be questioned about the presence of symptoms associated with anemia, such as fatigue, headache, and weakness, and whether there is a history of heavy menstrual bleeding or prior anemia. A medication history should include antibiotics; NSAIDs; chemotherapeutic, biologic, and supportive agents; and all over-the-counter medications and supplements. History of acute or viral infections is important. Transfusion history, immunologic disorders such as idiopathic thrombocytopenic purpura, and family history of bleeding abnormalities should be included. Patients’ nutritional status needs to be assessed to possibly identify any vitamin deficiencies, such vitamin B₁₂ and folic acid deficiencies (Rodriguez & Gobel, 2011). A complete thrombosis history, including the age at onset and the location and results of diagnostic examinations for the patient, as well as family members, is important. A history of VTE in one or more first-degree relatives is particularly important because it is suggestive of a hereditary defect or increased susceptibility for VTE disease (Bezemer, van der Meer, Eikenboom, Rosendaal, & Doggen, 2009).

A systematic physical examination focused on assessing for signs of bleeding follows the patient history. Bleeding within the central nervous system can be manifested by mental status changes, lethargy, restlessness, altered level of consciousness, seizures, coma, and changes in neurologic signs such as pupil size and reactivity, motor strength and coordination, and change in speech. Headache also may be present. Examination of the eyes and ears may reveal partial visual field loss, increased redness in the eyes, periorbital edema, and subconjunctival hemorrhage. The patient may report blurred vision and eye or ear pain. Examination of the nose, mouth, and throat may reveal petechiae on the nasal or oral mucosa, ulceration, gingivitis, or mucous membrane bleeding. Epistaxis may be present. Signs of bleeding manifested by the cardiovascular system include changes in the vital signs, color and temperature of all extremities, changes in the peripheral pulses, tachycardia, and/or hypotension. During examination of the pulmonary system, it is important to note changes in the respiratory rate and depth, dyspnea, tachypnea, shortness of breath, crackles, wheezing, orthopnea, hemoptysis, or cyanosis. Examination of the GI system could reveal increased or vague pain, blood around the rectum, tarry stools, and occult blood in the stool or hematemesis. Indications of bleeding in the genitourinary system are blood in the urine, dysuria, burning, frequency and pain with urination, decreased urine output, and a change in the character or amount of menses. Bleeding in the musculoskeletal system
could manifest as warm, tender, swollen joints with diminished mobility. Indications of bleeding in the integumentary system include signs of bruising, petechiae, purpura, ecchymoses, hematomas, pallor or jaundice, and oozing from injection sites, biopsy sites, central lines, catheters, and even nasogastric tubes (Rodriguez & Gobel, 2011).

Assessing for risk of VTE is important because half of the patients with VTE are asymptomatic. Information regarding conditions that could increase risk, such as recent surgery, trauma, heart failure, and immobility, should be discussed. Women should be questioned regarding their use of oral contraceptive medications. A complete cancer history including any previous incidence of VTE is important because recurrent thrombosis, despite therapeutic anticoagulation, is more common in patients with cancer (Landaw & Bauer, 2011). In a general physical examination, special attention should be directed to the vascular system, extremities, chest, heart, abdominal organs, and skin (Landaw & Bauer, 2011). Because many of the clinical manifestations and examination findings can be nonspecific, further diagnostic testing is required to confirm or exclude the diagnosis of VTE.

**Diagnostic Evaluation**

**Bleeding**

Many diagnostic tests are used to determine if bleeding is present. Hemocult tests of stool and excreta and urine dipstick are used to quantify microscopic hematuria. Actual volume measurement of melena or hematemesis is used for active blood loss (Friend & Pruett, 2004). Imaging scans also can be used to assess for internal bleeding. Laboratory values are the most commonly used tools to determine bleeding and coagulation status and include tests to determine platelet counts, bleeding times, D-dimer levels, and levels of specific coagulation factors. Hemoglobin and hematocrit values are used to monitor blood loss (Friend & Pruett, 2004). Patients with cancer may present with existing anemia and have reduced hemoglobin and hematocrit levels. However, a sudden drop in these levels could indicate an acute blood loss and should be treated immediately (Friend & Pruett, 2004).

Bleeding time can be measured by calculating the time it takes to stop bleeding from a small incision in the skin. Normal bleeding time varies from 1 to 9 minutes (Rodriguez & Gobel, 2011). Bleeding time is dependent on both the number of platelets and on how well the blood vessels function, especially the ability of the vessels to vasoconstrict. Prolonged bleeding time may result from alterations in either of these factors and may occur with thrombocytopenia, tumor infiltration of bone marrow, consumption of platelets in DIC, and use of medications that alter platelet function. Bone marrow aspiration is used to determine the etiology of thrombocytopenia by assessing whether the megakaryocytes in the marrow are normal or altered in number. If the
megakaryocytes are reduced in number within the bone marrow, the cause is related to primary thrombocytopenia or a reduced production of platelets. When the megakaryocytes are normal or elevated in the bone marrow, then the thrombocytopenia is a result of increased uptake or peripheral destruction of platelets (Friend & Pruett, 2004).

The platelet count, which quantifies the number of platelets in the blood volume, is the best gauge of possible bleeding in a patient with cancer. The Common Terminology Criteria for Adverse Events (National Cancer Institute Cancer Therapy Evaluation Program [NCI CTEP], 2010) grades a decreased platelet count from 1 to 5, with mild thrombocytopenia (grade 2) defined as a platelet count of less than 75,000/mm³ (see Table 1-4).

After a patient receives a platelet transfusion for thrombocytopenia, the response to the transfusion must be evaluated. A corrected count increment (CCI) is a formula based on a platelet count obtained 10 minutes to one hour after transfusion. The American Society of Clinical Oncology (ASCO) defines refractoriness as a CCI of less than 5,000/microliter on at least two sequential occasions (Schiffer et al., 2001). Although the CCI can be used, it often is not the most practical means of assessing response. This is because the formula for calculating CCI uses the number of platelets transfused, which often is not available. Therefore, a more common definition uses measurements of platelet recovery and platelet response to indicate refractoriness. Platelet recovery is defined as the increment in platelet count measured 10 minutes to one hour following transfusion. Platelet survival is evaluated by a platelet count obtained 18–24 hours after transfusion. Platelet refractoriness is considered to be present if a rise in the absolute platelet count of less

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<th>Table 1-4. Common Toxicity Criteria for Adverse Events: Platelet Count Decreased</th>
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than 10,000/microliter occurs after administration of a unit of platelets and/or a rapid return to pretransfusion levels is seen when evaluating both recovery and survival (Schiffer et al., 2001).

Besides laboratory tests, certain radiographic studies such as computed tomography (CT) scans, magnetic resonance imaging (MRI), x-rays, or ultrasounds can be used to determine whether any bleeding is present. Endoscopic examinations can be used to assess for bleeding in the upper or lower GI tract but would rarely be used for this purpose because any sort of invasive procedure could also put the patient at an increased risk for bleeding (Pereira & Phan, 2004).

**Thrombosis**

The American Academy of Family Physicians, the American College of Physicians, and the Institute for Clinical Systems Improvement all recommend the use of prediction rules to establish pretest probability of VTE (Borgstrom et al., 2012; Qaseem et al., 2007). The Wells prediction rules for DVT and PE are validated tools that are frequently used to determine the probability of VTE prior to performing additional diagnostic tests (see Table 1-5). In the Wells test for DVT, points are given based on patient assessment and symptoms (Qaseem et al., 2007). A low probability of DVT is defined as a score of ≤0, intermediate probability, 1–2, and high probability, ≥3. In patients with symptoms in both legs, the more symptomatic leg is used for scoring. There is also a prediction rule for PE. In this probability test, a score of 0–1 indicates low probability of PE, 2–6 is intermediate probability, and ≥7 is high probability (Qaseem et al., 2007).

Historically, when a patient has been shown to have a low pretest probability of VTE, a D-dimer test is the next step. The D-dimer has a high sensitivity for the presence of an acute thrombosis. The D-dimer can be used to exclude VTE with a high sensitivity for negative probability. In other words, patients with low pretest predictability and a negative D-dimer are considered to have DVT ruled out, and no further testing is needed (Borgstrom et al., 2012). However, studies confirming the use of D-dimer as predictive for VTE have not included large numbers of patients with cancer. One study using the Wells test and D-dimer for diagnosis of VTE stated that little difference existed between patients with and without cancer. However, the number of patients with cancer was found to have four times the number of symptomatic VTE at follow-up than patients without cancer. In addition, the number of false-positives in patients with cancer was three times higher (National Comprehensive Cancer Network [NCCN], 2011). For these reasons, NCCN recommends that further studies be completed involving patients with cancer. For PE, a chest radiograph, arterial blood gases (ABGs) and electrocardiogram (ECG) should be performed to rule out other disorders. Chest x-rays can show atelectasis or pleural-based infiltrates or effusions. ABGs can show hypoxemia and hypocapnia. ECG can show supraventricular arrhythmia, right axis deri-
vation, or cor pulmonale. If the D-dimer is positive, further testing including duplex ultrasound for both VTE and PE and chest CT angiography for PE should be completed (NCCN, 2011).

Patients with an intermediate to high pretest predictability for VTE should have a venous duplex ultrasound performed as the first test when DVT is suspected (Qaseem et al., 2007). D-dimer can be used in addition after negative ultrasound to determine whether further testing is needed. When DVT is suspected and D-dimer is positive despite negative ultrasound, then serial ultrasonography, CT venography, or contrast venography can be performed. Contrast venography has historically been considered the gold standard for accurate diagnosis. However, the several drawbacks of this method include cost, discomfort to the patient, limited availability, requirement of foot vein cannulation, use of IV contrast, and secondary emboli (Borgstrom et al., 2012).

### Table 1-5. Wells Prediction Rule for Diagnosing Deep Vein Thrombosis and Pulmonary Embolism

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<th>Wells Prediction Rule for Diagnosing Deep Vein Thrombosis and Pulmonary Embolism</th>
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Because of this, venography should be reserved for difficult diagnostic cases or to help distinguish between old clots and new clots.

When PE is suspected in the presence of an intermediate to high pretest predictability, noninvasive pulmonary vascular imaging including CT pulmonary angiography (CTPA) and ventilation/perfusion (VQ) scan is recommended as the initial radiologic evaluation (Borgstrom et al., 2012). Both CTPA and VQ scans have a high degree of sensitivity to diagnose PE; therefore, the choice of imaging modality depends on factors such as the availability of the test, the resolution of images obtained, underlying conditions including renal status, and the experience of the radiologist. Extra care should be taken when using dye in patients with renal insufficiency. CTPA has, in some areas, become easier to obtain than VQ scans. In addition, CTPA is more useful in patients with underlying cardiac disease and chronic obstructive pulmonary disease. When alternative diagnoses are likely, CTPA is especially beneficial because it can rule out PE and confirm other diagnoses in one test (Borgstrom et al., 2012).

**Treatment Modalities**

**Bleeding**

**Prophylaxis**

Transfusions of red blood cells, platelets, and plasma have been used effectively in patients with thrombocytopenia to prevent bleeding. Transfusions of red blood cells usually are initiated when the hemoglobin drops below 8 g/dl (grade 3 anemia [NCI CTEP, 2010]). Currently, no studies have been done that indicate at what level transfusions should be initiated to improve outcomes. However, the guidelines for several chemotherapy regimens require the platelet count to be at a certain level prior to administering the chemotherapy (Callow, Swindell, Randall, & Chopra, 2002; Heddle et al., 2006; Stanworth et al., 2004).

The transfusion of platelets plays an important role in bleeding prevention and management (Damron et al., 2009). Usually one unit of platelets can increase the count by 6,000–10,000 platelets per microliter of blood, but each individual case is unique, and the same results might not be seen in each individual. Patients with acute leukemia or solid tumors and those undergoing stem cell transplantation should maintain a platelet threshold of 10,000/microliter. Patients who are scheduled to undergo minor procedures and those with bladder tumors, necrotic tumors, and highly vascular tumors should have a threshold of 20,000/microliter of blood. Patients who will be undergoing any type of invasive procedure should have the platelet threshold at 40,000–50,000/microliter (Damron et al., 2009). Several factors can influence the effectiveness of platelet transfusions, including fever, sepsis, and hypersplenism. Another important factor in the effectiveness of platelet transfusions is
the proper storage of platelets to maintain their freshness and metabolic activity. After the platelets are obtained, the ideal administration time for the maximum effectiveness is within six hours. However, they can be stored for up to five days (Schiffer et al., 2001). Transfusion of plasma generally is reserved for patients with coagulation abnormalities who must undergo surgical procedures.

The administration of recombinant colony-stimulating growth factors has been used to reduce the negative hematopoietic effects of chemotherapy and radiation therapy by accelerating the recovery period. Recombinant human interleukin-11 (rhIL-11), erythropoietin, and recombinant thrombopoietin have all been used effectively to stimulate megakaryocyte proliferation. Several studies using rhIL-11 in patients with solid tumors, lymphoma, acute myeloid leukemia, and MDS have shown efficacy in the prevention of severe thrombocytopenia following myelosuppressive chemotherapy (Rodriguez & Gobel, 2011). To achieve maximum benefit, rhIL-11 should be initiated within 24 hours after chemotherapy is completed and continue for up to 21 days. This will increase platelet levels in five to nine days of administration, which should coincide with the expected chemotherapy-induced platelet nadir (Bhatia, Davenport, & Cairo, 2007). Although studies are limited regarding the use of erythropoietin for chemotherapy-induced thrombocytopenia, the administration of erythropoietin increases hemoglobin concentration and reduces the need for red blood cell transfusions in patients with anemia resulting from chemotherapy administration. Darbepoetin alfa, a growth factor derived with recombinant DNA technology, stimulates erythropoiesis. Because it has a longer half-life than erythropoietin, it can be given once weekly, whereas erythropoietin must be administered three times weekly (Cases, 2003).

**Treatment**

A variety of interventions may be used to manage bleeding in patients with cancer. The specific plan designed to treat bleeding is individualized for each patient and depends on many factors, including the underlying causes, the likelihood of reversing or controlling the bleeding etiology, the status of the malignant process, the goals of therapy, the patient’s comorbidities, and whether the treatment benefit outweighs risks (Pereira & Phan, 2004). If there is a benefit to treatment, then specific measures are put in place to control the bleeding. Treatments used to control bleeding include transfusions of blood products, vitamin K therapy, and mechanical measures. Other therapies include radiation treatments, endoscopic procedures, and even surgery, but these are usually used as a last resort because they could increase the risk of bleeding.

Transfusions reduce morbidity and death from thrombocytopenia and are likely to prevent and manage bleeding in patients with cancer who are actively bleeding (Damron et al., 2009). With normal splenic pooling, an average of four to six units is needed to control bleeding (Pereira & Phan, 2004). The traditional management of patients with HLA antibodies is to provide platelets
from HLA-matched donors. Unfortunately, for many patients, HLA-matched donors are unavailable. In this case, platelets from partially mismatched donors may provide adequate responses. Patients in whom alloimmunization alone is responsible for platelet refractoriness generally respond well to HLA-matched donor platelets. These platelets should be irradiated to prevent transfusion-associated graft-versus-host disease (Wang et al., 2012).

Red blood cell therapy is usually initiated when a patient’s hematocrit falls below 30% (Rodriguez & Gobel, 2011). In patients with cancer, decreased red blood cell production is usually caused by the disease process or to myelosuppressive therapy. One unit of red blood cells usually will increase the hematocrit by 3% and the hemoglobin by 1 g/dl in a 70 kg nonbleeding patient. Transfusion of packed red blood cells is used most often because it can provide more than 70% of the hematocrit of whole blood and only one-third of the plasma (Rodriguez & Gobel, 2011), thus minimizing fluid overload issues. As with any therapy, individual patient assessment is taken into consideration, including pulmonary or cardiac issues.

Human plasma, which is derived from whole blood products or plasmapheresis, is used to correct coagulopathy. Fresh frozen plasma commonly is given when a patient’s international normalized ratio (INR) level is greater than two times above baseline with an abnormal partial thromboplastin time level. Plasma can be used in patients who present with shock, severe bleeding, bleeding associated with an infection, and management of acute DIC. To obtain an adequate INR, large volumes of fresh frozen plasma would need to be infused. For this reason, it is not the treatment of choice in most cases. Typically, plasma is infused quickly so that the maximum plasma level is reached before any metabolic changes occur (Rodriguez & Gobel, 2011).

Vitamin K is necessary for the hepatic production of a number of clotting factors including factors II, VII, IX, and X. Patients who have small bowel disease or resection or biliary obstruction are prone to deficiencies of these clotting factors. Vitamin K therapy is effective if a deficiency of these factors or excessive warfarin therapy is implicated in bleeding in a patient with advanced cancer. The preferred route to administer vitamin K is orally, thus reducing the potential for additional bleeding or infection in an already compromised patient (Pereira & Phan, 2004).

Although not typically recommended for the control of bleeding in patients with cancer, vasopressin has been shown to be effective for control of lower GI bleeding. Vasopressin acts by causing severe splenic arteriolar constriction, which reduces blood flow, thus aiding in plug formation in the affected vessel. It is less effective in bleeding that is not arteriolar, and it requires close monitoring in an intensive care unit (Cagir, 2011).

Mechanical measures can be utilized if bleeding occurs, including applying direct steady pressure to the site of bleeding. When the site of bleeding is not directly exposed, mechanical pressure such as the insertion of a balloon catheter or nasal packing can be used, especially when dealing with epistaxis. It is very important, however, that extreme care be used when either remov-
ing or replacing packing so as to avoid disturbing the clot that has formed (Rodriguez & Gobel, 2011).

If the bleeding is from peripheral phlebotomy sites or central venous catheter sites, hemostatic bioabsorbable dressings can be applied to stop the bleeding (Rodriguez & Gobel, 2011). Other topical agents that can be used include absorbable gelatin, collagen, cellulose, fibrin sealants, and alginates (Samudrala, 2008).

When minor vascular bleeding caused by damaged capillaries is evident, it is imperative to treat the underlying malignancy. If anemia arises in this situation, then most often oral iron supplements will be used. Oral supplements are safe and can correct anemia within six weeks, but therapy may need to continue for up to six months for the iron stores to be adequately replaced (Jayakumar & Jayakumar, 2000).

### Coagulation

#### Prophylaxis

Three respected groups issuing medical guidelines—ASCO, the American College of Chest Physicians (ACCP), and NCCN—recommend routine thromboprophylaxis for patients with cancer who do not have contraindications to anticoagulation (Geerts et al., 2008; Lyman et al., 2007; NCCN, 2011). Contraindications to anticoagulation are those measures that put a patient at an increased risk for bleeding. These include clinically significant active or chronic bleeding, recent surgery with a high associated bleeding risk, thrombocytopenia or platelet dysfunction, and abnormalities associated with clotting factors such as those associated with prolonged prothrombin time or activated partial thromboplastin time (NCCN, 2011). Frequent reevaluation of these contraindications is recommended, as they can be temporary in many patients. A risk-benefit analysis is critical when determining whether to administer thromboprophylaxis to patients. Several studies have confirmed a generally low risk of major bleeding in patients with cancer who receive prophylaxis with LMWH, with no difference in risk of major bleeding noted between LMWH and unfractionated heparin (UFH) (Agnelli, Bergqvist, Cohen, Gallus, & Gent, 2005; Leonardi, McGory, & Ko, 2007; Rasmussen et al., 2006; Spyropoulos et al., 2008). All three guidelines recommend routine prophylaxis for patients with cancer who are undergoing surgical procedures and patients with cancer who are bedridden with an acute medical illness. These recommendations include both pharmacologic and mechanical prophylaxis.

The guidelines consider all adult hospitalized patients with a diagnosis or suspicion of cancer to be at risk for the development of VTE. In the absence of contraindications, they should be considered for pharmacologic prophylaxis with LMWH, UFH, or factor Xa inhibitors with or without the addition of venous compression devices (VCDs). For those with contraindications, mechanical prophylaxis with the use of VCDs, including graduated compres-
sion stockings and/or intermittent pneumatic compression and vena cava filters (NCCN, 2011), should be initiated. Mechanical prophylaxis should not be used alone except in the presence of contraindications to pharmacologic prophylaxis. The advantage of VCDs is that they can be used in patients with an increased risk for bleeding. However, disadvantages are that they can interfere with ambulation and must be worn almost continuously to be effective. The placement of inferior vena cava filters has the advantage of preventing PE in patients at high risk for VTE where anticoagulation is contraindicated. However, vena cava filters do not prevent DVT and have been associated with an increased risk of recurrent DVT. The use of inferior vena cava filters cannot substitute for antithrombotic therapy in patients with cancer and should be used only if there is an absolute contraindication to anticoagulation or failure of anticoagulation (NCCN, 2011). Anticoagulation should be resumed as soon as the clinical picture allows. VTE prophylaxis for at-risk ambulatory patients should be considered. If the patient has had cancer surgery, especially pelvic or abdominal surgery, VTE prophylaxis is recommended for up to four weeks postoperatively (NCCN, 2011).

**Treatment**

Guidelines for the treatment of VTE from ACCP, ASCO, and NCCN are based on the findings of three major studies (Hull et al., 2006; Lee et al., 2003; Meyer et al., 2002). Based on the findings of these studies, ACCP guidelines recommend LMWH for the first three to six months of long-term anticoagulant therapy in patients with cancer and DVT. Subsequent anticoagulation with vitamin K antagonists or LMWH until cancer is resolved is recommended (Geerts et al., 2008). ASCO guidelines state that LMWH is preferred for the first 5–10 days of anticoagulation and given for at least six months for long-term therapy, but vitamin K antagonists may be used if LMWH is not available (Lyman et al., 2007). Similarly, NCCN guidelines recommend LMWH for at least three months for treatment of VTE and recommend continuing indefinite anticoagulation for patients with active cancer or other persistent risk factors (NCCN, 2011). ACCP guidelines (Geerts et al., 2008) also recommend the use of graduated elastic support stockings in patients who have had symptomatic proximal DVT, to begin as soon as the patient or caregiver is able to apply the stockings and continuing for at least two years.

**Heparin-Induced Thrombocytopenia**

Both UFH and LMWH are associated with heparin-induced thrombocytopenia (HIT). HIT is an immune-mediated reaction to heparins. It occurs in 2%–3% of patients treated with UFH and less than 1% of patients treated with LMWH (Borgstrom et al., 2012). Paradoxically, patients with HIT have an increased risk for developing VTE for up to 100 days following diagnosis. Patients with a history of HIT should not be treated with UFH or LMWH. HIT should be suspected in patients who develop skin lesion reac-
tions at the injection site, have a systemic reaction to a bolus administration of heparin, or experience a greater than 50% decrease in platelet count from baseline laboratory values while on heparin (Borgstrom et al., 2012). Another form of HIT, delayed onset, typically presents as thromboembolic complications one to two weeks after the last dose of LMWH or UFH. These patients usually have mild or moderate thrombocytopenia. If HIT is not suspected, the patient is typically rechallenged with heparin, thus leading to worsening of the thrombosis and thrombocytopenia. If HIT is suspected, heparin therapy should be stopped while antibody testing is completed. While waiting for antibody test results, the patient can be effectively treated with direct thrombin inhibitors (DTIs). If HIT is suspected in a patient on warfarin therapy, the warfarin should be stopped and reversed with vitamin K therapy and DTIs (Borgstrom et al., 2012). Low-dose therapy with warfarin can be restarted while the patient is being treated with DTIs after the platelet count has significantly improved and there is clinical improvement in the thrombosis (Borgstrom et al., 2012).

**Nursing Management**

Nurses have a key role in the prevention and management of bleeding in patients with cancer and need to be able to recognize the early signs and symptoms of bleeding and VTE through astute observation and physical assessment. Table 1-6 provides an overview of the physical examinations and nursing interventions in the care of patients who have active bleeding or are at risk for bleeding.

The vital signs, hemodynamic status, oxygenation, and fluid status are closely monitored in patients with a risk for bleeding. All unnecessary procedures should be avoided, including intramuscular injections, subcutaneous injections, rectal temperatures and suppositories, and indwelling catheters. Sites where injections are given could put the patient at risk for hematomas and could lead to infection. If an injection must be given, the smallest gauge needle should be used and direct pressure applied for several minutes followed by application of a pressure dressing to avoid a hematoma. Cold compresses also can be used to induce vasoconstriction (Rodriguez & Gobel, 2011).

Nurses must ensure that patients with a risk for bleeding who present with a cough have an antitussive medication ordered. Medications with codeine are recommended to help minimize the induction of bleeding related to coughing. Antiemetics are important to avoid nausea and vomiting. Bowel strain from constipation could result in bleeding, so laxatives and stool softeners should be used to avoid constipation.

Care should be taken when performing dressing changes. Interventions to reduce bleeding from wounds include gentle dressing removal; use of nonadherent dressings, moist wound products, and multiple layer dressings; and only a minimal number of dressing changes and packing (Damron et al., 2009).
Table 1-6. Physical Examination and Care of Patients With Actual or Potential Bleeding

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Table 1-6. Physical Examination and Care of Patients With Actual or Potential Bleeding *(Continued)*

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Preventive measures for VTE for all hospitalized patients are a crucial part of the nurse’s role. Positioning is an important aspect of prevention. Avoiding prolonged sitting and elevating the patient’s legs when in bed helps to promote venous return. Daily assessment of extremities for pain, erythema, and size discrepancy is vital. Proper use of compression devices, incentive spirometry, adequate hydration, and early ambulation are encouraged to prevent VTE. The nurse must vigilantly monitor patients who are immobilized or who have had their activity restricted for unexplained tachypnea, tachycardia, and restlessness. These signs should not be simply attributed to anxiety unless a physical reason has been ruled out.

Attention during anticoagulation is warranted to prevent significant bleeding complications. If the nurse encounters a change in mental status or new focal neurologic deficits in a patient receiving thrombolytics, intracranial hemorrhage must be eliminated as a possible cause. Figure 1-2 lists nursing interventions related to VTE.

**Patient and Caregiver Education**

Because bleeding is a very common and potentially fatal event in patients with cancer, it is imperative that patients and caregivers are made aware of strategies to help prevent bleeding and receive instructions about what to do if it occurs. The nurse should instruct them to do an environmental check at home to identify and remove bump and fall risks, such as throw rugs, to remove clutter from rooms and pathways, and to wear either shoes or slippers at all times to minimize the potential for injury. To maintain good skin integrity, patients should be taught to use lotion that prevents dryness and breaks in skin and to avoid the use of adhesive tape, which causes skin trauma; only paper tape should be used. The mouth and

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**Figure 1-2. Nursing Interventions for Patients at Risk for Venous Thromboembolism**

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gums of thrombocytopenic patients are susceptible to injury; therefore, patients should be instructed to apply nonpetroleum lubricant to the lips and gums to keep them moist and to use a soft-bristled toothbrush to avoid trauma. Substances that can irritate the tissues of the mouth and gums are to be avoided, including hot, spicy foods, alcoholic beverages, and mouthwashes that contain alcohol. To prevent bleeding from the nose, the patient should be taught to clean the nares with a cotton swab or tissue and to avoid vigorous nose blowing (Friend & Pruett, 2004). The use of saline nose drops and sprays, as well as a small amount of moisturizing ointment such as petroleum jelly inside the nostrils, will help to prevent nosebleeds (Romito & O’Connor, 2011).

Bleeding events can be very distressing for patients and caregivers, so excellent communication should be maintained between them and the nurse, and a plan should be developed in case an acute bleeding episode occurs. To help reduce some of the psychological distress from bleeding, it is recommended that dark towels be used and a basin be placed next to the patient’s bed to use if bleeding occurs (Gagnon et al., 1998). Instruction to put the patient in a lateral position for comfort and to avoid suffocation in the case of a massive bleed is critical (Gagnon et al., 1998).

Education regarding VTE should include information on the clinical condition itself as well as treatments and therapies implemented and potential lifestyle changes that could reduce a patient’s risk. Treatments that require teaching include early and frequent ambulation, the use of an incentive spirometer, and proper and timely use of compression devices. When anticoagulation therapy is initiated, education regarding the administration and side effects of each medication is required. Patients or caregivers may need to learn to give subcutaneous injections if LMWH is to be continued after discharge. Signs and symptom of bleeding, including bleeding precautions, should be included in education, as well as the signs of subsequent or recurrent VTE. Education provided to patients and caregivers is essential to helping the patients to maintain compliance with their ongoing anticoagulation therapy. Patients who are continuing on warfarin therapy will need to be instructed to limit foods high in vitamin K, such as dark green vegetables and apricots, to prevent decreased warfarin action. Patients should be taught that their blood counts will need to be monitored in order to keep their INR between 2 and 3 when on warfarin therapy (U.S. National Library of Medicine PubMed Health, 2010). Because patients with a history of VTE are at greater risk for subsequent VTE, they should be instructed to keep well hydrated and stretch every hour during confined travel (Kahn et al., 2012).

Thorough education for patients and caregivers can not only help them to recognize potential problems but also can help to reduce patients’ risk for bleeding and recurrent VTE. Good communication, including possible interventions, needs to be in place in order to keep patients and their caregivers calm and focused should bleeding or VTE occur.
Conclusion

Bleeding in patients with cancer may be caused by a variety of underlying factors, including the disease process and cancer therapies, all of which can contribute to reducing the quantity and functional quality of platelets and initiating alterations in clotting factors. The first step in managing bleeding is to identify the underlying causes of the bleeding. Determining the type and origin of bleeding will help to direct treatment. Although several treatments are effective for bleeding, the individual patient’s condition, goals of treatment, and comorbidities must be considered before deciding on a treatment plan.

Patients with cancer have an increased risk of developing VTE, which is associated with considerable morbidity and mortality. Hospitalized medical and surgical patients with cancer are at an increased risk for VTE and should be considered for pharmacologic prophylaxis if no contraindications are present. Consideration of prophylactic anticoagulation in patients with cancer must always balance the risk of VTE with the increased risk of bleeding. Proper patient and family education regarding the risk of bleeding, as well as the signs and symptoms of both bleeding and VTE recurrence, is paramount in the care of patients with cancer.

References


