

Heart and Lung Complications

Assessment and prevention of venous thromboembolism and cardiovascular disease in patients with multiple myeloma

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BACKGROUND: Venous thromboembolism (VTE) and cardiovascular (CV) disease can occur in patients with multiple myeloma. Although VTE and CV disease are separate medical conditions, they can be serious and even life-threatening.

OBJECTIVES: The objectives of this article are to describe risk factors for cancer-associated VTE, describe the influence of CV disease on patients with multiple myeloma, and review the approaches to VTE and CV disease identification and treatment.

METHODS: PubMed and CINAHL® databases were used to identify literature to describe VTE and CV in patients diagnosed with multiple myeloma.

FINDINGS: When present in patients with multiple myeloma, VTE and CV disease can limit patient tolerance for myeloma treatment and, therefore, decrease therapeutic options.

KEYWORDS

thrombosis; blood clots; multiple myeloma; cardiac disease; cardiotoxicity

DIGITAL OBJECT IDENTIFIER

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VENOUS THROMBOEMBOLISM (VTE) AND CARDIOVASCULAR (CV) DISEASE commonly occur in patients with cancer, specifically multiple myeloma (MM) (Ritts, Lenihan, & Cornell, 2016). Although VTE and CV disease are separate medical conditions, they are equally serious, each with the potential to be life-threatening. Like the general American population, patients with MM have a high prevalence of preexisting comorbid CV conditions, including hyperlipidemia and hypertension, and non-CV conditions such as diabetes (National Heart Lung and Blood Institute, 2012; Palumbo et al., 2008). In patients with MM, VTE is six times more likely to occur with dexamethasone combined with immunomodulatory agents, such as lenalidomide, thalidomide, or pomalidomide (Lyman et al., 2015; Palumbo et al., 2008). When present in patients with MM, VTE and CV disease can limit patient tolerance for antimyeloma treatment and, therefore, decrease therapeutic options. This article aims to (a) describe risk factors for cancer-associated VTE, (b) describe the influence of CV disease on patients with MM, and (c) review the approaches to VTE and CV disease identification and treatment. As new agents become available for MM, the prevention and management of VTE and CV complications should remain a priority for the long-term health of patients.

Venous Thromboembolism

Although thrombosis can occur anywhere in the venous system, VTE most frequently occurs in lower extremities as a deep vein thrombosis (DVT). DVT treatment is intended to prevent circulation of the VTE to the lung, where it becomes a pulmonary embolism (PE). The cause of VTE in MM is often multifactorial, involving the interaction of clinical risk factors, such as immobility and hypercoagulability from treatment, and inherent risk factors for thrombosis, such as activation of procoagulant factors and inflammation (Kristinsson, 2010). In several clinical trials, the use of immunomodulatory drugs in MM has been associated with an increased risk of VTE (Rajkumar et al., 2010; Weber et al., 2007). For patients with VTE in the first 10 years of a MM diagnosis, mortality is two times higher than in patients who do not have VTE. Patients who have VTE in the first year of a MM diagnosis have a three times higher mortality rate (Kristinsson, Pfeiffer, Bjorkholm, Schulman, & Landgren, 2012).

Pathophysiology of Venous Thromboembolism

Specific systemic conditions predispose individuals with cancer to VTE development. These conditions were first described by Rudolph Virchow in 1859 and are known as Virchow's Triad, which consists of hypercoagulability, vessel wall or endothelial injury, and stasis (Kesieme, Kesieme, Jebbin, Irekpita, & Dongo, 2011).

Prothrombotic mechanisms respond to the presence of a tumor, causing inflammation, necrosis, and hemodynamic changes, which can also be exacerbated by MM therapy (Kristinsson, 2010). In addition, clot-promoting molecules with procoagulant and fibrinolytic activities are secreted by tumor cells, causing an interaction with endothelial cells. This plays an important role in pathogenesis. In addition, venous stasis reduces the clearance of activating coagulation factors, causing endothelial cell damage and increasing the risk for VTE (Elyamany, Alzahrani, & Bukhary, 2014; Kesieme et al., 2011).

Immunomodulatory drugs have various anti-angiogenic and anti-inflammatory effects that can alter the interaction between the tumor cells and the bone marrow microenvironment. Although the exact reason why these drugs increase the risk of VTE is unknown, it is thought that they can enhance the expression of tissue factor and vascular endothelial growth factor and, by downregulating thrombospondin, cause cytokine-mediated activated protein C resistance (Kristinsson, Bjorkholm, Schulman, & Landgren, 2011).

Risk Factors for Venous Thromboembolism in Multiple Myeloma

VTE incidence is higher among patients diagnosed with monoclonal gammopathy of undetermined significance (an asymptomatic premalignant clonal plasma cell or lymphoplasmacytic proliferative disorder associated with an increased risk of developing MM

FIGURE 1.

VENOUS THROMBOEMBOLISM RISK FACTORS

- Recent history of immobilization or bed rest
- Recent surgery
- Older age
- History of venous thromboembolism
- Obesity
- Male gender
- Trauma, particularly to the lower extremities
- Malignancy
- Medications: immunomodulatory drugs, oral contraceptives, erythropoietin
- Pregnancy or postpartum period
- History of stroke
- Presence of central venous line

Note. Based on information from Brown et al., 2016; Fahrni et al., 2015; Heit et al., 2016; Palumbo et al., 2008; Story, 2014.

FIGURE 2.

MEDICAL AND FAMILY HISTORY RISK FACTORS FOR VENOUS THROMBOEMBOLISM

- Complete thrombosis history (Was thrombosis idiopathic or provoked by surgery, a long car or airplane ride, or immobility?)
- Pregnancy
- History of vascular disease, nephrotic syndrome, malignancy, polycythemia vera, heparin-induced thrombocytopenia, thyroid disease, systemic lupus erythematosus
- Antiphospholipid syndromes
- Sickle cell disease
- History of recent infection or inflammation
- Recent exposure to dehydration
- Recent prolonged travel by air or automobile
- Trauma or bone fracture
- Varicose veins
- Family history of venous thromboembolism or known inherited thrombophilia, such as Factor V Leiden, prothrombin gene *G20210A* mutation, and protein C or S

Note. Based on information from Fahrni et al., 2015; Heit et al., 2016; Kesieme et al., 2011.

or lymphoma) and MM than in the general population (Gregarson et al., 2011; Kristinsson et al., 2011). Risk factors for VTE are listed in Figure 1. The risk of VTE is also increased in inherited and noninherited thrombophilia conditions, such as factor V Leiden, prothrombin *G20210A* mutation, protein C or protein S deficiency, and antithrombin deficiency (Fahrni, Husmann, Gretener, & Keo, 2015; Heit, Spencer, & White, 2016).

Venous Thromboembolism Risk Factors: Medication

Several medications increase the risk of VTE. Patients treated with immunomodulatory drugs (IMiDs), such as thalidomide, lenalidomide, or pomalidomide, or with steroids and/or chemotherapy are also at significant risk of developing VTE. When higher doses of dexamethasone are used, the risk of VTE increases significantly. Another medication that is associated with increased incidence of VTE is erythropoietin, which may be used in the setting of anemia in patients with MM (Anaissie et al., 2012).

In a study comparing low- and high-dose dexamethasone in combination with lenalidomide, the incidence of VTE was 12% in the low-dose dexamethasone group and 26% in the high-dose dexamethasone group. The low-dose dexamethasone dose was 40 mg weekly on days 1, 8, and 15. The high-dose dexamethasone was 40 mg on days 1–4, 9–12, and 17–20 (Rajkumar et al., 2010). In a study by Bat et al. (2005), the incidence of VTE was 58% in patients with MM who were treated with thalidomide and an anthracycline but did not receive thrombosis prophylaxis medication. Anticogulant therapy can also reduce VTE incidence rates. When aspirin was

added at the start of the thalidomide-containing regimen, the incidence rate of VTE decreased to about 19% (Baz et al., 2008).

A retrospective chart review reported that the overall incidence of VTE in patients on IMiD therapy was 9.7% (Dede & Pruemer, 2016). One goal of the study by Dede and Pruemer (2016) was to compare the rate of VTE when national VTE prophylaxis guidelines were and were not followed. The national guidelines include the use of aspirin in patients with less than two VTE risk factors, and low-molecular-weight heparin (LMWH) for patients with two or more VTE risk factors (Palumbo et al., 2008). When national guidelines were followed, VTE occurred at a rate of 4.8%. When the guidelines were not followed, VTE occurred in 12.2% of the patients. The rate of VTE in patients not receiving thromboprophylaxis was 23.1%. Of note, no patients taking LMWH or warfarin developed VTE. Of the patients taking aspirin, 7.9% developed VTE (Dede & Pruemer, 2016).

Assessment of Venous Thromboembolism Risk

Signs and Symptoms

Information in the patient's medical and family history is vital for identifying risk factors for VTE (see Figure 2). Careful review of a patient's medical history, elicitation of his or her subjective review of systems, and completion of a comprehensive physical examination are all necessary to identify the subtle findings that may lead to the diagnosis of VTE. Combining the subjective and objective data in the patient encounter with laboratory and radiologic assessment is key to a prompt diagnosis. For example, the physical examination may reveal a thrombosed vein or hard palpable cord in the calf, posterior knee, or thigh that is erythematous, painful, and consistent with DVT. The respiratory assessment may reveal the inability to take deep breaths, tachypnea,

FIGURE 4.

LABORATORY TESTS FOR THROMBOPHILIA

DEFICIENCY OF COAGULATION FACTOR INHIBITORS

- Protein S deficiency
- Protein C deficiency
- Antithrombin III deficiency

INCREASED LEVEL OR FUNCTION OF THE COAGULATION FACTORS

- Activated protein C resistance
- Factor V Leiden
- Prothrombin gene mutation
- Increased levels of Factors VIII, IX, or XI
- Increased lupus anticoagulant
- Dysfibrinogenemias

Note. Based on information from Story, 2014.

and shallow breaths, which are consistent with PE. Signs and symptoms of DVT and PE are presented in Figure 3.

Laboratory Tests

On completion of the history and physical examination, further diagnostic testing, including laboratory tests and imaging, may be indicated. Laboratory tests that should be considered include electrolytes, D-dimer, prothrombin time, international normalized ratio, partial thromboplastin time, and antithrombin level. Of note, although an increased D-dimer level is a sensitive indicator of an acute thrombotic event, the level is also increased in nonthrombotic clinical situations, such as pregnancy, infection, malignancy, atrial fibrillation, stroke, and other inflammatory conditions (Bates et al., 2012; Pulivarthi & Gurram, 2014). Testing for inherited thrombophilia conditions may be indicated, but the results will not change the initial treatment for a patient who is diagnosed with VTE. Figure 4 lists laboratory testing for specific inherited thrombophilia conditions. A hematologist may need to evaluate the patient before ordering laboratory tests.

Diagnosis of Venous Thromboembolism

Appropriate and prompt assessment of the patient with suspected VTE is vital in making a rapid diagnosis. Radiologic studies that can identify DVT or PE include Doppler ultrasonography, contrast venography, computed tomography angiography, ventilation perfusion lung scan, and magnetic resonance venography. The standard approach to diagnosing for suspected DVT is Doppler ultrasound (Bates et al., 2012). Although computerized tomography angiography can accurately diagnose PE and pelvic vein or inferior vena cava thrombosis, it requires the use of contrast. Magnetic resonance venography may be performed without contrast to detect PE, can differentiate chronic from acute thrombus, and can be used to avoid

FIGURE 3.

SIGNS AND SYMPTOMS OF PULMONARY EMBOLISM AND DEEP VEIN THROMBOSIS

PULMONARY EMBOLISM

- Dyspnea or tachypnea
- Chest discomfort
- Tachycardia
- Low-grade fever
- Pleural rub

DEEP VEIN THROMBOSIS

- Unilateral swollen, erythematous, and warm extremity
- Dull ache, pain, or tight feeling over affected area
- Low-grade fever
- Distension of superficial venous collateral vessels
- Positive Homan's sign

Note. Based on information from Rome et al., 2008; Story, 2014.

radiation in pregnant women (Gaitini, 2007). Ventilation perfusion lung scan is useful only in patients with normal chest radiographs and is typically used when computed tomography angiography is contraindicated or inconclusive (Thompson & Kabrhel, 2017)

The Wells criteria is a scoring system used to determine the risk of PE or DVT before radiologic testing is done (see Table 1), and to determine subsequent treatment or follow-up imaging. A trial of 501 patients (78 with cancer) was conducted in Canada from 1994–1996 to determine the need for serial ultrasound testing of patients suspected of having DVT. Patients with a Wells score greater than 3 were at a high risk for DVT, whereas patients with a score of 0 had a low likelihood of DVT (Wells et al., 1997).

Prevention and Treatment Strategies

Prevention of VTE is essential for patients at risk for thrombosis. A heightened awareness of VTE prevention has occurred and many standards of care for VTE prevention have been implemented. Figure 5 presents several of the available strategies for VTE prevention.

Anticoagulation medications, such as LMWH, warfarin, and fondaparinux, can be used to prevent VTE (Kearon et al., 2012). Patients with MM who take IMiDs should take anticoagulation medication to prevent VTE. The use of oral anticoagulants, such as dabigatran, rivaroxaban, and apixaban, is controversial for VTE prevention in malignancy and is currently under investigation (Streiff et al., 2016).

TABLE 1.
WELLS CRITERIA FOR THROMBOSIS RISK

| VARIABLE | SCORE |
|---|-------|
| Active cancer (treated within six months or palliative) | 1 |
| Paralysis, paresis, or recent plaster immobilization of lower extremities | 1 |
| Recently bedridden for more than three days or major surgery within 12 weeks | 1 |
| Localized tenderness along the distribution of the deep venous system | 1 |
| Entire leg swollen | 1 |
| Calf swelling greater than 3 cm when compared with asymptomatic leg (measured at 10 cm below tibial tuberosity) | 1 |
| Pitting edema | 1 |
| Collateral superficial veins | 1 |
| Alternative diagnosis as likely or greater than that of deep vein thrombosis | -2 |

Note. Total score of 0 indicates low risk, a score of 1–2 indicates moderate risk, and a score of 3 or higher indicates high risk.
Note. From "Value of Assessment of Pretest Probability of Deep-Vein Thrombosis in Clinical Management," by P.S. Wells, D.R. Anderson, J. Bormanis, F. Guy, M. Mitchell, L. Gray, . . . B. Lewandowski, 1997, *The Lancet*, 350, p. 1,797. Copyright 2017 by Elsevier Limited. Reprinted with permission.

FIGURE 5.
VENOUS THROMBOEMBOLISM PREVENTION

- Exercise regimen to increase mobility and prevent stasis
- Compression stockings and devices
- Weight control
- Dehydration prevention
- Cardiac management
- Aspirin/anticoagulation prophylaxis for long car rides or airplane flights, pregnancy, and surgery
- Aspirin/anticoagulation while taking immunomodulatory drugs
- Avoidance of medications that increase the risk of venous thromboembolism (oral contraceptives, erythropoietin)

Note. Based on information from Bates et al., 2012; Elias et al., 2016; Moheimani & Jackson, 2011; Rome et al., 2008.

The treatment of VTE is changing, with many options now available for patients. In the setting of acute VTE, LMWH and unfractionated heparin (UFH) should be considered. Oral anticoagulation with medications, such as warfarin, can be used in the patient with MM but should be used with LMWH (enoxaparin, dalteparin), UFH, or fondaparinux until the international normalized ratio is in a therapeutic range that is within the range of 2–3 (normal range is 0.9–1.3). Direct oral anticoagulant (DOAC) medications are not well established for VTE in malignancy and are currently under investigation (ClinicalTrials.gov, 2014; Streff et al., 2016). Rivaroxaban has been studied in a large, randomized clinical trial of patients with symptomatic VTE, and could be considered for long-term anticoagulation of patients with MM (Einstein Investigators, 2010). Dabigatran is a IIa (thrombin) inhibitor and rivaroxaban and apixaban are Xa inhibitors. Patients often prefer the new oral agents because laboratory monitoring and dietary restriction are not necessary. However, a drawback to the new oral anticoagulants is their long half-life compared to heparin or LMWH, which can lead to prolonged uncontrolled bleeding (Babilonia & Trujillo, 2014). No commercially available medications are available to reverse the anticoagulation effects of the new oral anticoagulants, although activated prothrombin complex concentrate medications have shown promise in initial studies (Awad & Cocchio, 2013). Table 2 reviews anticoagulation medications used to treat or prevent VTE.

Anticoagulation medication should continue while patients with MM are treated with IMiDs, such as lenalidomide, thalidomide, or pomalidomide (Lyman et al., 2015; Palumbo et al., 2008). Patients should be prescribed anticoagulation for six months and then reevaluated for risk of recurrent VTE and/or bleeding (Lyman et al., 2015). Patients with MM and VTE should be monitored by an anticoagulation service if they receive warfarin or are seen by a vascular medicine specialist, as indicated. Blood monitoring is

necessary for patients on warfarin for accurate dosing. The schedule of blood work is determined by the specialist(s) managing the warfarin dosing.

MM is an inherently hypercoagulable state that is complicated by modifiable and nonmodifiable risk factors. The science of VTE has progressed, with newer agents and methods to stratify risk. The etiology of VTE, like many conditions, is multifactorial. Risk factors for development of VTE, thrombosis assessment, and diagnostic criteria should be carefully evaluated when a patient requires treatment for VTE.

Evidence-Based Recommendations

The International Myeloma Foundation Nurse Leadership Board (NLB) used Melnyk and Fineout-Overholt's (2011) levels of evidence as a systematic framework for the appraisal and grading of the NLB's consensus statements and evidence-based recommendations.

LEVEL OF EVIDENCE I

- Nurses should teach patients with MM about their increased risk for DVT, measures they can take to prevent DVT (ambulation to prevent venous stasis and avoidance of dehydration), the signs and symptoms of DVT (such as edema and pain in the extremity), and the need to report any DVT symptoms immediately (Lyman et al., 2015; Rome, Doss, Miller, & Westphal, 2008).
- Nurses and clinicians should use risk stratification to determine patients' risks of developing VTE. Factors that increase VTE risk include a history of prior VTE, surgery, anthracycline chemotherapy, high-dose corticosteroids, hospitalization, and heart disease. All high-risk patients who take IMiDs should also take aspirin, LMWH, warfarin, or fondaparinux prophylaxis. Preventive treatment should be initiated only after considering each patient's risk of bleeding versus thrombosis (Lyman et al., 2015; Rome et al., 2008).

TABLE 2.
ANTICOAGULATION MEDICATIONS USED TO TREAT OR PREVENT VENOUS THROMBOEMBOLISM

| MEDICATION | CATEGORY | USE IN MALIGNANCIES | NURSING CONSIDERATIONS |
|------------------------|---|---|--|
| Dabigatran | Direct oral anticoagulant IIa Inhibitors | Use in malignancy is under investigation. | <ul style="list-style-type: none"> ■ Major side effect is bleeding. ■ Bleeding cannot be reversed. ■ Long half-life ■ Renally excreted ■ Blood levels do not require monitoring. |
| Enoxaparin, dalteparin | Low-molecular-weight heparin | Commonly used in patients diagnosed with cancer | <ul style="list-style-type: none"> ■ Major side effect is bleeding. ■ Hold with thrombocytopenia. ■ Patient should be taught how to perform SC injections. ■ Patients should not take nonsteroidal anti-inflammatory drugs. ■ Monitor renal status with serum creatinine levels. |
| Fondaparinux | Pentasaccharide; selective anti-Xa activity | Used in patients with cancer; used when patients develop heparin-induced thrombocytopenia | <ul style="list-style-type: none"> ■ Major side effect is bleeding. ■ Hold with thrombocytopenia. ■ Long half-life |
| Heparin | Unfractionated heparin | Used in the inpatient setting for all patients, including patients with cancer | <ul style="list-style-type: none"> ■ Major side effect is bleeding. ■ Monitor for heparin-induced thrombocytopenia. ■ Hold with thrombocytopenia. ■ Administered via IV or SC ■ Not commonly used in the homecare setting ■ Monitored by aPTT ■ Very short half-life |
| Rivaroxaban, apixaban | Direct oral anticoagulant Xa Inhibitors | Use in malignancy is under investigation. | <ul style="list-style-type: none"> ■ Major side effect is bleeding. ■ Long half-life ■ Does not require blood monitoring ■ Rivaroxaban is mostly renally excreted. ■ Apixaban has renal and hepatic excretion. ■ Monitor renal function. ■ Bleeding cannot be reversed; however, aPCC is under investigation. |
| Warfarin | Oral vitamin K agonists | Used in patients with cancer | <ul style="list-style-type: none"> ■ Major side effect is bleeding. ■ Numerous medication interactions ■ Hold with thrombocytopenia. ■ Requires INR/PT blood monitoring ■ Can be reversed with vitamin K ■ Dose is dependent on oral intake of food high in vitamin K. ■ Long half-life |

aPCC—activated prothrombin complex concentrate; aPTT—activated partial thromboplastin time; INR—international normalized ratio; PT—prothrombin time; SC—subcutaneous
Note. Based on information from Awad & Cocchio, 2013; Piran & Schulman, 2016; Streiff et al., 2016.

- For all patients with a suspected VTE, a subjective history of illness, targeted physical examination, laboratory testing, and radiologic imaging are indicated. If a DVT is suspected, individuals should be screened with a Doppler ultrasound of the extremity. If a PE is suspected, a ventilation perfusion lung scan is safer than contrast computed tomography angiography scan in patients with MM. In patients with evolving DVT or suspected PE, anticoagulation is recommended with preference for LMWH, if creatinine clearance greater than 30 ml per minute, or with warfarin, which carries a higher bleeding risk (Lyman et al., 2015; Palumbo et al., 2008; Rome et al., 2008).
- All patients should be taught to rapidly identify the signs and symptoms of bleeding. Clinicians should advise patients to stop taking aspirin or anticoagulation when their platelets are below a clinically significant level and prior to surgery. Patients with platelet counts less than $100 \times 10^9/L$ should be monitored closely, and if the count falls below $50 \times 10^9/L$, thromboprophylaxis should be held until the platelet count recovers to above $50 \times 10^9/L$, except in very high-risk cases or during acute VTE episodes. The need for anticoagulation in patients with thrombocytopenia should be considered on a case-by-case basis (Carrier, Khorana, Zwicker, Noble, & Lee, 2013).

FIGURE 6.**CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH MULTIPLE MYELOMA****CORONARY ARTERY DISEASE RISK FACTORS**

- Smoking
- Family history (first-degree relative: male younger than age 55 years or female younger than age 65 years)
- Hypertension
- Obesity
- Dyslipidemia
- Sedentary lifestyle
- Diabetes mellitus

CORONARY ARTERY DISEASE RISK EQUIVALENTS

- Non-coronary atherosclerotic disease
- Chronic kidney disease

MULTIPLE MYELOMA-SPECIFIC CARDIAC RISK FACTORS

- Prior anthracycline exposure
- Prior stem cell treatment
- Heavily pretreated (having received many prior lines of chemotherapy)
- Concurrent cardiac amyloid light-chain amyloidosis
- Concurrent dexamethasone treatment

Note. From "Cardiac Considerations for Modern Multiple Myeloma Therapies," by A.J. Ritts, D.J. Lenihan, & R.F. Cornell, 2016. Retrieved from <http://bit.ly/2vCrBAa>. Copyright 2017 by American College of Cardiology. Reprinted with permission.

LEVEL OF EVIDENCE II

- DOACs provide an oral option for anticoagulation delivery, but currently little evidence supports their use in VTE prevention and treatment in patients with MM (Lyman et al., 2015; Man, Morris, Brown, Palkimas, & Davidson, 2016).

Cardiotoxicity

CV disease and cancer are the two leading causes of death in the United States, creating a clinically challenging scenario when these two diseases intersect. Cardiovascular toxicity, defined by the National Cancer Institute as direct damage to heart tissue, is a potential short- or long-term complication from anticancer therapy (Shelburne et al., 2014). Figure 6 presents cardiovascular risk factors in patients with MM.

The evolution of new therapies for the treatment of MM has increased the overall survival of patients. However, longer survival exposes patients to adverse side effects of cytotoxic agents and may lead to lethal side effects. Exposure to chemotherapy medications can increase the risk of irreversible, clinically significant cardiac dysfunction. For this reason, many patients with MM now face an increase in treatment-related comorbidities, including cardiac toxicities. Of note, the gain in life expectancy because of anticancer therapy might be countered by an increase in mortality from cardiac problems, such as heart failure, myocardial ischemia, arrhythmias, hypertension, and thromboembolism (Shelburne et al., 2014).

The incidence of cardiotoxicity depends on various features of oncologic therapies. The type of drug, dose administered during each chemotherapy cycle, cumulative dose, schedule of administration, route of administration, combination with other cardiotoxic drugs or association with radiation therapy, and patient health history (age, presence of CV risk factors, previous CV disease, and prior mediastinal radiation therapy) all play an integral role in causing potential cardiotoxicity (Hahn, Lenihan, & Ky, 2014; Yeh & Bickford, 2009).

Anticancer drugs influence or disrupt pathways that are centrally involved in cell survival, cell growth, inflammatory activation, and angiogenesis (Minami, Matsumoto, & Horiuchi, 2010). Cardiac toxicity may be a dose-limiting factor throughout a patient's clinical course and treatment. Healthcare providers (RNs, advanced practitioners, physician assistants) need to understand the possible risks for cardiac toxicity and the signs and symptoms of cardiac events (see Figure 7).

Definition of Chemotherapy-Induced Cardiotoxicity

Chemotherapy may induce cardiotoxicity through several mechanisms, including direct injury to myocardial cells and indirect injury to cardiac tissue through effects on the coagulation system, changes in cardiac rhythm, induction of hypertension, and myocardial and/or pericardial inflammation (Florescu, Cinteza, & Vinereanu, 2013). Cardiotoxicity is a general term used for

toxicity that affects the heart but is without a clear definition. Although the National Comprehensive Cancer Network (2017) defines cardiac toxicity as damage to the heart by harmful chemicals, Florescu et al. (2013) defines chemotherapy-induced cardiotoxicity according to the presence of reduced left-ventricular ejection fraction (LVEF) and/or signs or symptoms of heart failure. Specifically, cardiotoxicity is defined by Florescu et al. (2013) in the presence of at least one of the following: (a) global or specific interventricular reduction in LVEF; (b) symptoms or signs of heart failure; or (c) LVEF reduction to 5%–55% of base-

line with heart failure signs or symptoms, or LVEF reduction to 10%–55% of baseline without heart failure signs or symptoms.

Chemotherapy and Immunotherapy Agents and Toxicities

MM treatments include chemotherapeutic and immunotherapy agents that have the potential to cause cardiac toxicities. Table 3 presents immunotherapy- and chemotherapy-associated cardiac toxicities and nursing considerations for patients with cardiac abnormalities. The following sections highlight classifications of these agents and treatments that may prompt cardiac toxicities.

FIGURE 7.

PATIENT TIP SHEET: PREVENTING BLOOD CLOTS AND CARDIOVASCULAR EVENTS

Patients with cancer, particularly MM, are at high risk of developing blood clots (thromboembolic events) and heart problems, or experiencing worsening of preexisting heart problems. If you have MM, you may be able to prevent blood clots or improve your outcomes if you get blood clots or have heart problems. You can learn how to recognize the symptoms of blood clots early enough to improve the likelihood of successful treatment and decrease the likelihood of complications. Since treatments for MM can increase the risk for blood clots and heart disease, your healthcare provider may change your treatment based on your symptoms.

TYPES OF THROMBOEMBOLIC EVENTS

- **DVT:** A small blood clot in the arm, leg, hand, or foot; DVT is the most common type of thromboembolic event. Signs of DVT include swelling, aching, pain, tightness, or a lump in the arm, leg, hand, or foot; fast heartbeat; and veins larger than usual (distended).
- **PE:** A blood clot that travels to the lungs. Signs of PE include anxiety, fast heartbeat and fast breathing, chest pain, new onset of shortness of breath, and coughing up blood.
- **Cerebral infarction (stroke):** The result of a blood clot that travels to the brain. Signs include change in emotional or mental behavior and confusion, severe headache, chest pain, loss of coordination, and sudden numbness or weakness.

TESTS THAT YOU MAY UNDERGO

To see if you may have a blood clot, your nurse or healthcare provider will perform tests, which may include:

- An ultrasound of your arms or legs if they are swollen or painful
- A test called a ventilation/perfusion scan, or VQ scan, that checks to see if there is a blockage in blood flow in your lungs
- A CT scan to look for a blood clot in your lungs. Tell your healthcare provider if you have kidney problems; the IV contrast dye may be hard on your kidneys.
- Electrocardiogram or echocardiogram

TREATMENT OF BLOOD CLOTS

- DVT, PE, and stroke are considered medical emergencies. Report any symptoms to your healthcare provider immediately.
- The treatments or medications you receive will be based on your individual risk factors.

- You may need to receive medications to prevent new blood clots from forming.
- Low-dose aspirin may be suggested if you have no risk factors for blood clots or only one risk factor.
- Pills or injectable anti-clotting drugs may be prescribed if you have more than one risk factor. Risk factors include lack of activity, obesity, smoking, personal or family history of blood clots, taking estrogen compounds (hormone replacement), taking drugs to increase the amount of red blood cells (e.g., erythropoietin, epoetin alfa, darbepoetin alfa), recent surgery, and prolonged air travel or sitting for long periods of time.

WAYS TO REDUCE YOUR BLOOD CLOT RISK

- Exercise, such as walking, ankle circles, and knee-to-chest lifts
- Weight loss
- Smoking cessation
- Take medications prescribed by your healthcare providers.
- Notify your healthcare providers if you have ever been diagnosed with a blood clot.
- Report concerning signs and symptoms immediately to your healthcare providers, including shortness of breath, chest pain or tightness, cough, or swelling of an extremity.

WAYS TO PREVENT HEART DISEASE

- The American Heart Association recommends regular activity or exercise to decrease your risk of blood clots and stroke and lower your blood pressure.
- Stop smoking if you already smoke, or do not start.
- Eat a healthy diet with more fruits and vegetables than oils, fats, and carbohydrates. People with a lower body mass index are less likely to have heart problems, diabetes, or high blood pressure.
- See a primary care provider for regular blood pressure, diabetes, and cholesterol monitoring.
- Remember that most patients with MM are living longer than ever. By staying as active as possible and leading a heart healthy lifestyle, you can reduce your risk of complications and stay as healthy as possible.

CT—computed tomography; DVT—deep vein thrombosis; MM—multiple myeloma; PE—pulmonary embolism

Note. Based on information from Elias et al., 2016; Rome et al., 2008; Story, 2015.

PROTEASOME INHIBITORS

Bortezomib is a proteasome inhibitor approved for the treatment of MM, and carfilzomib is a proteasome inhibitor used in the treatment of refractory or relapsing MM. Proteasome inhibitors cause cell death by interfering with the breakdown of cell cycle proteins and coronary vasospasm by impairing endothelial nitric oxide synthase activity. In several case reports, clinical heart failure has been reported in 2%–5% of proteasome inhibitor recipients (Hamo & Bloom, 2015).

ALKYLATING AGENTS

Cyclophosphamide is an alkylating agent that kills rapidly dividing cells. Depending on the dose of cyclophosphamide, it may be associated with the development of acute myopericarditis and left ventricular dysfunction in 7%–22% of patients (Hamo & Bloom, 2015; Yeh & Bickford, 2009).

ANTHRACYCLINES

Anthracyclines, such as doxorubicin, act as antitumor agents by interfering with protein synthesis, producing reactive oxygen, and inhibiting DNA repair. Doxorubicin causes myocardial damage by interacting with topoisomerase II, an enzyme that is present on cardiac myocytes. Anthracyclines cause left ventricular dysfunction, which occurs with lifetime exposure to more than 450 mg/m² (Hamo & Bloom, 2015; Yeh & Bickford, 2009).

RADIATION THERAPY

In radiation therapy, high-energy particles interrupt cell growth and kill cells, including cancer cells and cardiac myocytes. When

IMPLICATIONS FOR PRACTICE

- Understand that patients with multiple myeloma (MM) are at risk for developing disease- and treatment-related venous thromboembolism (VTE) and cardiovascular (CV) complications.
- Recognize risk factors and educate patients about prevention and treatment strategies for VTE and CV complications.
- Risk-stratify all patients with MM for VTE and CV complications at the time of diagnosis.

radiation is directed at the mediastinum, it can cause pericarditis, atherosclerosis, valve dysfunction, heart failure, and fatal cardiovascular events. The risk of myocardial damage is increased with high radiation doses, long exposure times, and the use of cytotoxic therapy (Hamo & Bloom, 2015).

IMMUNOMODULATOR DRUGS

The use of thalidomide, lenalidomide, and pomalidomide in patients with cancer is commonly associated with the development of thromboembolic complications, including thrombotic coronary artery disease (Kristinsson et al., 2012; Palumbo & Palladino, 2012).

Clinical Follow Up and Monitoring of Patients

Healthcare providers should monitor patients for side effects of any treatment and keep accurate records of cumulative treatments given over time. All patients undergoing chemotherapy should have prior evaluation and assessment of CV risk factors or comorbidities. CV side effects of chemotherapy may vary from mild, transient, asymptomatic reduction in LVEF to cardiac death.

Chemotherapy-induced cardiotoxicity can be monitored using plasma concentrations of troponin I and N-terminal pro-B-type

TABLE 3.
CHEMOTHERAPY AND IMMUNOTHERAPY ASSOCIATED WITH MULTIPLE MYELOMA CARDIOVASCULAR TOXICITY

| CHEMOTHERAPY CATEGORY | CHEMOTHERAPY DRUGS | CARDIAC TOXICITY | NURSING CONSIDERATIONS |
|---|--|--|--|
| Alkylating agents | Cyclophosphamide | HF, LVD, pericardial effusion, myopericarditis; venous thromboembolism | Baseline MUGA or echocardiogram |
| | Cisplatin | | |
| Angiogenesis inhibitors | Lenalidomide, pomalidomide | Venous thromboembolism | Prophylaxis with aspirin or LMWH or warfarin is recommended for those with two or more multiple myeloma-related risk factors. Bradycardia is defined as heart rate less than 60 bpm. |
| | Thalidomide | Venous thromboembolism, bradycardia | |
| Anthracycline | Doxorubicin | LVD, dilated cardiomyopathy, HF | Baseline MUGA or echocardiogram |
| Antibody-based tyrosine kinase inhibitors | Bevacizumab, trastuzumab | HF, cardiomyopathy, arterial thrombotic event, HTN, LVD | Baseline MUGA or echocardiogram |
| Proteasome inhibitor | Bortezomib, carfilzomib | HF, LVD | Baseline MUGA or echocardiogram |
| Small molecule tyrosine inhibitor | Dasatinib, lapatinib, imatinib mesylate, sunitinib | HF, LVD, myocardial ischemia, HTN | Baseline MUGA or echocardiogram |

HF—heart failure; HTN—hypertension; LMWH—low-molecular-weight heparin; LVD—left ventricular dysfunction; MUGA—multigated acquisition scan
Note. Based on information from Hamo & Bloom, 2015; Yeh & Bickford, 2009.

natriuretic peptide, which are released from overloaded myocardial tissue (Minami et al., 2010). Echocardiography is commonly used before cancer therapy is started to determine baseline cardiac function and may be used to detect cardiotoxicity. Patients undergoing cancer therapy should be routinely evaluated for echocardiography abnormalities that could indicate cardiotoxicity (Bovelli, Plataniotis, & Roila, 2010).

General Recommendations for Cardiovascular Health

The American Heart Association has set forth goals for the CV health of people in the United States. These health goals should apply to patients with MM to minimize morbidities, particularly as patients live longer. In general, smoking, physical activity, blood pressure, cholesterol, glucose, and body mass index are all modifiable risk factors (Lloyd-Jones et al., 2010; Ritts et al., 2016).

Evidence-Based Recommendations

LEVEL OF EVIDENCE I

- Because patients with MM are at risk of developing CV disease, they should be evaluated by a cardiologist early in the course of their disease if they have a history of CV disease or develop cardiac events during therapy (Ritts et al., 2016).
- All healthcare providers should assess symptoms of chemotherapy- and radiation-induced vascular and cardiac changes. Dysrhythmias, angina, dyspnea at rest and with exertion, acute tachypnea, lower extremity pain, hypotension, diaphoresis, venous jugular distention, peripheral edema, and echocardiography changes should be evaluated promptly (Loerzel & Dow, 2003).
- Patients should be educated about healthy behaviors, such as smoking cessation, weight loss, and diet. Modifiable risk factors for CV disease should be addressed (Lloyd-Jones et al., 2010).

Conclusion

Traditional and novel anticancer agents have the potential to induce VTE and CV toxicity. The dose and duration of certain types of chemotherapy may have to be limited if cardiac toxicity develops during treatment (Loerzel & Dow, 2003). Thorough patient assessments must be performed at intervals throughout the disease course and should focus on prior cardiac history, potential cardiotoxicity, and thromboembolic risk.

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