Acute promyelocytic leukemia (APL) was previously described by Hillestad (1957) as a fatal disease with an aggressive course and short duration. Pathologically, the disease was characterized by numerous promyelocytes in the blood and bleeding tendencies from a low fibrinogen level and platelet count. Since that time, multiple events have occurred in clinical practice and scientific medicine that have revolutionized the diagnosis and treatment and improved the prognosis for APL, with most patients now being cured from this once-fatal disease (Degos, 2003).

This article provides the oncology nurse with an overview of APL, including the epidemiology and pathophysiology that distinguishes APL from other types of acute leukemia. Clinical presentation and diagnostic workup for patients suspected of having APL will be reviewed, as will the treatment course. Nursing implications and management will be provided related to potential treatment complications specific to APL, including coagulopathies, differentiation syndrome, and QT prolongation with the use of arsenic trioxide, as well as several complications that can occur in any patient with leukemia, such as infection, hyperleukocytosis, tumor lysis, and increased intracranial pressure.

Acute promyelocytic leukemia (APL) was first described by Hillestad (1957) as a fatal disease with an aggressive course and short duration. Pathologically, the disease was characterized by numerous promyelocytes in the blood and bleeding tendencies from a low fibrinogen level and platelet count. Since that time, multiple events have occurred in clinical practice and scientific medicine that have revolutionized the diagnosis and treatment and improved the prognosis for APL, with most patients now being cured from this once-fatal disease (Degos, 2003).

This article provides the oncology nurse with an overview of APL, including the epidemiology and pathophysiology that distinguishes APL from other types of acute leukemia. Clinical presentation and diagnostic workup for patients suspected of having APL will be reviewed, as will the treatment course. Nursing implications and management will be provided related to potential treatment complications specific to APL, including coagulopathies, differentiation syndrome, and QT prolongation with the use of arsenic trioxide, as well as several complications that can occur in any patient with leukemia, such as infection, hyperleukocytosis, tumor lysis, and increased intracranial pressure.

Acute promyelocytic leukemia (APL) was previously considered a highly lethal form of acute myeloid leukemia (AML) but, because of research and drug development, is now the most curable subtype of adult AML.

APL is pathologically different from other types of AML because of its specific morphology and abnormality on chromosomes 15 and 17.

The complications of coagulopathy, differentiation syndrome, and QT prolongation are seen more commonly in patients diagnosed in APL compared to other types of leukemia.

The complications of coagulopathy, differentiation syndrome, and QT prolongation are seen more commonly in patients diagnosed in APL compared to other types of leukemia.
occur in any patient with leukemia, such as infection, hyperleukocytosis, tumor lysis, and increased intracranial pressure.

Epidemiology

The American Cancer Society (2010) estimated that 12,330 new cases of acute myeloid leukemia (AML) occurred in the United States in 2010. Of these cases, only a small percentage will have the morphologic characteristics that would be classified as APL. Until 1957, APL had not been distinguished from other types of acute leukemia, so its actual incidence was unclear (Matasar, Ritchie, Consedine, Magai, & Neugut, 2006; Ribeiro & Rego, 2006). Current reports estimate that the number of new cases of APL per year in the United States could be in the range of 600–800 (Ribeiro & Rego, 2006; Sanz et al., 2009; Yamamoto & Goodman, 2008). One study in Los Angeles County, between 1980–1995, documented 2,222 cases of AML and, of these, 107 (4.8%) were APL (Douer, 2003; Ribeiro & Rego, 2006). This figure is slightly less than the incidence range of 5%–15% reported in many large clinical trials in the United States (Ribeiro & Rego, 2006; Tallman & Altman, 2008).

Some studies have suggested that an increased incidence of APL is seen in patients of Latin American ethnicity. Of the AML cases reported in Latin American countries, around 20%–25% are classified as APL (Douer et al., 1996; Matasar et al., 2006). However, because this finding is still somewhat controversial, Sanz et al. (2009) recommended additional research into the possible increased incidence in Latin American populations.

The age distribution of patients with APL is different from other forms of AML. Most patients with APL are adults aged 20–50. APL is not typically a pediatric AML, as few children and teenagers develop this disease. In addition, patients older than 60 are not commonly affected (Ribeiro & Rego, 2006; Vickers, Jackson, & Taylor, 2000).

Few additional confirmed risk factors have been identified. Obesity may contribute to the incidence of APL, as people with an increased body mass index may be at greater risk. According to Douer (2003), no environmental factors have been identified as contributing to the incidence of APL.

Secondary or treatment-related APL (tAPL) develops after prior exposure to radiation or chemotherapy (Anderson et al., 2002; Beaumont et al., 2003; Bosca, Pascual, Casanova, Coret, & Sanz, 2008; Mistry et al., 2005; Pederson-Bjergaard, 2005; Pulsoni et al., 2002; Ribeiro & Rego, 2006; Smith et al., 2003). However, information on tAPL is limited. According to Beaumont et al. (2003) and Sanz et al. (2009), an increase in reported cases has been noted, with the incidence seemingly increasing in survivors with a history of breast cancer, non-Hodgkin lymphoma, and Hodgkin lymphoma. The drugs commonly associated with tAPL are topoisomerase-II inhibitors such as mitoxantrone and epirubicin. Reports also describe TAP occurring after treatment with radiation therapy (Anderson et al., 2002; Beaumont et al., 2003; Bosca et al., 2008; Mistry et al., 2005; Pederson-Bjergaard, 2005; Pulsoni et al., 2002; Ribeiro & Rego, 2006; Smith et al., 2003). Treatment for patients with tAPL should not be different from a de novo APL, with the exception of patients who have received an anthracycline (Sanz et al., 2009). Treatment with arsenic trioxide and all-trans retinoic acid (ATRA) should be considered instead (Estey et al., 2006).

Pathophysiology

APL is classified as the M3 subtype of AML by the French-American-British classification system (Bennet et al., 1985). A key characteristic is the presence of atypical promyelocytes in the bone marrow and peripheral blood (see Figure 1).

APL is distinguished pathologically from other types of AML because of its specific morphology and chromosome abnormality (Wang & Chen, 2008). Researchers have identified three morphologic variants of APL: hypergranular, hypogranular, and basophilic microgranular (Degos, 2003). The main variants differ in their clinical presentation, prognosis, and morphologic
appearance. The hypergranular form is the most common variant, representing about 75% of APL cases (Sainty et al., 2000). The bone marrow contains larger than usual abnormal promyelocytes with pleomorphic nuclei and cytoplasm containing coarse, large granules with abundant Auer rods often found in bundles (Sainty et al., 2000) (see Figures 2 and 3). The peripheral white blood cell count often is low, and patients often experience coagulation disorders (Bennett, Parker, & Ludlam, 1976; Degos, 2003). The hypogranular variant occurs about 25% of the time and is characterized by atypical promyelocytes with bilobed nuclei and the absence of visible granules (see Figure 4). Unlike patients with hypergranular disease, patients with hypogranular disease usually have a higher white blood cell count at presentation with coagulopathy (Bennett et al., 1980; Degos, 2003). The very rare variant form, basophilic microgranular, was first described by McKenna, Parkin, Bloomfield, Sundberg, and Brunning in 1982 and is characterized by a shorter remission. The leukemia cells were described as “small hyperbasophilic promyelocytes” with many Auer rods (p. 201).

Cytogenetically, APL is typically characterized by a chromosome abnormality that involves a balanced reciprocal translocation of the long arms of chromosomes 15 and 17 (Wang & Chen, 2008). Other gene rearrangements may occur and, of these, the most common is between chromosomes 11 and 17 or 5 and 17, and also are diagnostic of APL (Wang & Chen, 2008). The exchange between the chromosomes occurs without loss of chromosomal material and occurs between the promyelocyte leukemia (PML) gene on chromosome 15 and the retinoid acid receptor-alpha (RAR-α) gene on chromosome 17, creating an abnormal fusion protein called PML-RAR-α (Lo-Coco & Ammatuna, 2006; Rowley, Golomb, & Dougherty, 1977; Wang & Chen, 2008; Wu, 2002). The PML gene is thought to be involved with apoptosis and tumor suppression, whereas the RAR-α gene is mainly expressed in hematopoietic cells and has an important role in regulating gene expression related to myeloid differen-

tiation (Wu, 2002). Together, this fusion prevents transcription of genes necessary for developing myeloid cells to differentiate past the promyelocyte differentiation stage. This results in abnormal promyelocytes proliferating and accumulating in the bone marrow and peripheral blood. The leukemic promyelocytes lead to some of the signs and symptoms associated with the coagulopathy often seen in APL.

Diagnosis

Clinical Presentation

The presentation of APL can be subtle, with many patients presenting with days to weeks of nonspecific symptoms. Patients usually present with signs and symptoms that reflect a particular cytopenia (see Table 1). Patients with APL often present with bleeding and thrombosis, so a quick diagnosis is critical.

Diagnostic Workup

Guidelines have been established by both the National Comprehensive Cancer Network (NCCN, 2009) and the National Guideline Clearinghouse (Milligan et al., 2006) entailing recommendations for a comprehensive workup (see Figure 5). A diagnosis of APL must be quickly made because the treatment is different from other subtypes of AML. A careful history and physical examination should be performed with attention placed on assessing for signs and symptoms of bleeding and thrombosis. Laboratory tests should include a complete blood count, complete metabolic panel, uric acid, lactate dehydrogenase, and, if an APL diagnosis seems possible, a disseminated intravascular coagulation (DIC) screen (which may include prothrombin time/international normalized ratio, partial thromboplastin time, fibrinogen, and domain dimer) should be considered. The bone marrow aspiration and biopsy should be sent for cytogenetics and molecular diagnostic studies for PML-RAR-α (Sanz et al., 2009). NCCN (2009) also recommends evaluation of the patient...
Treatment of Newly Diagnosed Patients

APL is a highly malignant form of AML. It requires prompt treatment and is considered a medical emergency. The treatment for APL is distinct from other types of AML and may last one to two years. Treatment is divided into three different phases: induction, consolidation, and maintenance.

Induction

The overall goal of induction therapy is to reduce leukemia burden to below the cytologically detectable level. For patients newly diagnosed with suspected APL, the initial goal also must be to reduce the risk of severe bleeding and death, which often is seen during induction therapy precipitated by the malignant promyelocytes (de la Serna et al., 2008; Fenaux et al., 1992). To decrease mortality, induction treatment with ATRA must be started immediately in patients with suspected APL (Sanz et al., 2009). ATRA will work to produce granulocytes by differentiation of malignant promyelocyte blasts to granulocytes, thereby helping to reverse the coagulopathy often seen in patients with APL (Roche Laboratories, 2003).

According to Sanz et al. (2009), a diagnosis of APL does not need to be confirmed to begin patients on ATRA, but should be continued until the diagnosis is made at the genetic level. If the diagnosis is not confirmed, ATRA is discontinued and treatment is changed to an appropriate AML regimen. If the diagnosis is confirmed, treatment is continued with ATRA and additional chemotherapy administration is started as soon after the first ATRA dose as possible (Fenaux et al., 1999; Milligan et al., 2006).

Combination treatment with concurrent ATRA and anthracycline-based chemotherapy is considered a standard approach for induction therapy. This combination leads to complete remission rates in 80%-95% of patients, which was confirmed in several multicenter, randomized trials (Asou et al., 2007; Burnett, Grimwade, Solomon, Wheatley, & Goldstone, 1999; de la Serna et al., 2008; Fenaux et al., 1993, 1999; Sanz et al., 2004). The best type of anthracycline to be used during induction therapy has not been confirmed in the literature as no study has directly compared anthracycline options. Studies have combined ATRA with daunorubicin and cytarabine or with idarubicin (de la Serna et al., 2008; Fenaux et al., 1993; Tallman et al., 1997). For patients with high-risk disease, cytarabine has been used in their induction regimen to increase possibility of a remission (Adès et al., 2008; Lo-Coco et al., 2004, NCCN, 2009). The choice of chemotherapy agents often is left up to the provider and his or her experience. Prospective, randomized, clinical trials are needed to answer this question.

Patients who should not receive standard induction therapy include those who have received anthracycline-based therapy in the past, patients with a history of cardiac issues, or patients who have other contraindications for anthracycline-containing chemotherapy, such as being older than 80 years or having several comorbidities (Estey et al., 2006; Sanz et al., 2009).

Table 1. Clinical Presentation of Acute Promyelocytic Leukemia (APL)

<table>
<thead>
<tr>
<th>FINDINGS</th>
<th>NURSING INTERVENTION</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia: weakness, fatigue, pallor, tachycardia</td>
<td>Monitor laboratory results and administer blood products as indicated.</td>
<td>Frequent</td>
</tr>
<tr>
<td>Neutropenia: fever, infection, excessive sweating</td>
<td>Assess for potential causes of fever; initiate antibiotic, antifungal, and antiviral coverage; obtain laboratory work; include blood cultures; perform a chest x-ray, urine analysis, or urine culture and sensitivity.</td>
<td>Frequently related to infection; rarely related to leukemia</td>
</tr>
<tr>
<td>Thrombocytopenia: bruising, bleeding, ecchymoses, petechiae, retinal hemorrhages, epistaxis, bleeding gums, menstrual irregularity</td>
<td>Physical examination and laboratory check of complete blood count</td>
<td>Frequent</td>
</tr>
<tr>
<td>Oropharynx soreness, oral candidiasis, herpetic lesions, leukemic involvement</td>
<td>Thorough oropharynx examination</td>
<td>Frequent</td>
</tr>
<tr>
<td>Abdominal pain, fullness, splenomegaly, hepatomegaly</td>
<td>Physical examination with attention to abdominal examination</td>
<td>Rare in APL</td>
</tr>
<tr>
<td>Central nervous system involvement, headaches, irritability, vomiting, cranial nerve palsies, seizures, papilledema</td>
<td>Physical examination with attention to neurologic examination, visual changes, cranial nerve palsies, headaches</td>
<td>Rare, common in patients with hyperleukocytosis</td>
</tr>
<tr>
<td>Cutaneous sores and leukemia cutis</td>
<td>Integumentary evaluation</td>
<td>Rare in APL</td>
</tr>
<tr>
<td>Leukemia cells in bone marrow and bone pain</td>
<td>Rule out other causes of joint pain (i.e., gout, arthritis, or infection).</td>
<td>Rare in APL</td>
</tr>
</tbody>
</table>

Note: Based on information from Freireich, 2008.

for other comorbidities as well as factors such as prior treatment with chemotherapy or cardiac issues that may influence treatment decision making.

Special attention to white blood cell (WBC) and platelet counts also is important in the diagnostic workup and management of APL. According to Sanz et al. (2000), patients can be divided into three prognostic categories based on the WBC and platelet count. Each category correlates with the patient’s risk for relapse: low, intermediate, and high. Low-risk patients are defined as having a WBC count of less than or equal to 10 x 10^9/L and a platelet count greater than 40 x 10^9/L. These patients have an extremely low risk of relapse and, therefore, a less intense chemotherapy regimen may be selected. The intermediate-risk category is defined as having a WBC count of less than or equal to 10 x 10^9/L and a platelet count less than 40 x 10^9/L. Finally, the high-risk category is defined as having a WBC count of greater than 10 x 10^9/L (no platelet count is described). Patients with high risk would likely benefit from a more intense chemotherapy regimen.
ATRA plus arsenic trioxide may be considered for these patients (NCCN, 2009; Sanz et al., 2009).

Patients who achieve a complete remission with induction therapy proceed directly to consolidation therapy (Sanz et al., 2009; Tallman, Nabhan, Feusner, & Rowe, 2002). Patients who have drug-resistant disease or do not achieve a complete response should be treated for refractory disease. ATRA plus or minus arsenic trioxide, gemtuzumab, hematopoietic stem cell transplantation, and other investigational drugs are all options for these patients (NCCN, 2009; Sanz, Tallman, & Lo-Coco, 2005).

Consolidation

The goal of consolidation therapy is to destroy undetectable leukemia cells that survived induction therapy. Patients who received at least two more cycles of ATRA plus anthracycline-based chemotherapy (daunorubicin or idarubicin) achieved a molecular remission around 95% of the time (Sanz, Martin, & Lo-Coco, 2003). Patients who were exceptions during induction and received arsenic trioxide plus ATRA should continue this in consolidation (NCCN, 2009), as the NCCN recommends consistency throughout a treatment course. If an induction regimen is chosen from one clinical trial, treatment should continue into the consolidation and maintenance phases of the schedule from the same trial. High-risk patients should receive at least one cycle of cytarabine during consolidation (Sanz et al., 2004).

When consolidation has been completed, the patient’s response to treatment is evaluated with a bone marrow biopsy sample using reverse transcription polymerase chain reaction (RT-PCR) to look for PML-RARα and to evaluate the patient for a molecular remission (NCCN, 2009). A bone marrow biopsy is typically conducted at the end of consolidation to avoid confusion about the perceived lack of response to therapy that may occur when the patient’s response is evaluated at the usual day 10–14 bone marrow biopsy for patients with AML (Diverio et al., 1998; Jurac et al., 2007).

Maintenance

Several studies (Fenaux et al., 1999; Sanz et al., 2000, 2004) suggested that patients who have achieved a complete response after consolidation should continue on maintenance therapy consisting of one to two years of ATRA, possibly combined with 6-mercaptopurine and methotrexate (NCCN, 2009).

NCCN (2009) recommended that, during maintenance therapy, the patient be monitored by RT-PCR approximately every three months for two years. This can be done using a peripheral blood specimen or a bone marrow specimen. Additional monitoring includes monthly complete blood count and complete metabolic panel to identify any drug-related toxicity. Myelosuppression may be seen with the use of 6-mercaptopurine and methotrexate. Also, an increase in liver function studies may be seen with any of the three medications (Chan et al., 2007). Dose delays and adjustments may be necessary depending on the severity of myelosuppression or abnormal liver enzymes. These adjustments or delays are not standardized but are, instead, based on institutional protocols or physician judgment.

Disease and Treatment Complication Management

Coagulopathy

APL-associated consumptive coagulopathy is very intricate and may involve several processes, including DIC, fibrinolysis, and proteolysis (Stein et al., 2009). DIC is initiated by the release of tissue factor with procoagulant activity from the cytoplasm of leukemic promyelocytes (Lungstrom & Emerson, 2010). This procoagulant activity on the cell membrane is unique to APL and induces thrombin generation and the proteolytic activity in the cytoplasm (Gralnick & Abrell, 1973). This combination is thought to be an attributing factor to the coagulopathy seen in this patient population. Other factors may exacerbate coagulopathy, such as chemotherapy administration of a cytotoxic agent that causes destruction of the cells and release of cytokines and procoagulants into the bloodstream. Infections (viral, bacterial, or fungal) also can cause coagulopathy from DIC, thrombocytopenia, and vascular damage (Barbui & Falanga, 2001; Stein et al., 2009).

Clotting disorders are extremely common in patients with APL; about 85% of patients will experience coagulopathies (Ezzone, 2006; Holmes-Gobel, 2000). Therefore, healthcare providers must recognize this potentially fatal complication and start treatment immediately. Management of coagulopathies in patients with APL is very individualized. Focus should be placed on initiation of treatment with ATRA and chemotherapy to treat the underlying disease process.

ATRA, a vitamin A derivative, promotes differentiation and decreases proliferation of leukemic promyelocytes, allowing for growth of normal hematopoietic cells (Chan et al., 2007). Using ATRA during the remission-induction phase of therapy not only produces a high number of complete remissions, but a rapid
<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>SIGNS AND SYMPTOMS</th>
<th>ASSESSMENT AND DIAGNOSTICS</th>
<th>NURSING IMPLICATIONS AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding related to coagulopathy</td>
<td>Cardiovascular: tachycardia, hypotension, peripheral edema, and slow capillary refill</td>
<td>Vital signs, frequent assessments via physical examinations (with attention to symptoms). Assess for bleeding and for environmental issues that may relate to bruising (i.e., falls, pets, or activities). Complete blood count, platelets, fibrinogen degradation products, D-dimer, fibrinogen, PT/INR, PTT, peripheral blood smear, factor VII, and antithrombin III</td>
<td>Treatment of underlying cause; support with blood product, fresh frozen plasma, cryoprecipitate, and fibrinogen transfusions; minimize invasive procedures; and monitor vital signs. Heparin therapy is contraindicated in acute promyelocytic leukemia. Start ATRA therapy immediately.</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal: melena, hematemesis, rectal bleeding from hemorrhoids, and abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genitourinary: hematuria, vaginal bleeding, and reduced urine output</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HEENT: gingival bleeding, epistaxis, and scleral hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Integumentary: petechiae, purpura, ecchymosis, oozing from open areas, and a cool, clammy feeling</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurologic: headaches and altered level of consciousness and mental status</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary: hemoptysis, hypoxia, dyspnea, pulmonary congestion, use of accessory muscles to breathe, rales, and tachypnea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiation syndrome</td>
<td>Fever, dyspnea, acute respiratory distress, shortness of breath, fluid retention (lower extremity edema), weight gain, and hypotension</td>
<td>Vital signs, weight, oxygen saturation, and physical examination with attention to pulmonary and cardiac systems Complete blood count, platelet count, white blood cells (greater than 10,000/mcl), basic metabolic panel, and renal insufficiency Chest x-ray evaluating for pulmonary infiltrate, congestive heart failure, and pleural and pericardial effusions</td>
<td>Hold the ATRA and arsenic trioxide until severe symptoms, such as renal insufficiency or respiratory distress, resolve. May need to dose reduce when resuming medication. Dexamethasone 10 mg every 12 hours for at least three days or until symptoms resolve. May be used prophylactically in patients with a high white blood cell count.</td>
</tr>
<tr>
<td></td>
<td>Often reflect infectious and hemorrhagic complications, respiratory symptoms from exertional dyspnea to severe respiratory distress, neurologic symptoms from mild confusion to coma, and symptoms of a thrombosis</td>
<td>Vital signs and pulse oximetry; physical examination with attention to neurologic issues and to symptoms that would suggest infection Complete blood count and platelet count (with differential), CMP, PT/INR, PTT, and D-dimer Chest x-ray; if indicated, arterial blood gas and, if fever is present, workup is performed as for an infection.</td>
<td>Leukapheresis is not used as it may stimulate the coagulopathy; start immediate treatment with chemotherapy, ATRA, and steroids; treatment-related hyperleukocytosis may occur after starting arsenic trioxide. Careful observation is recommended. If reduction of white blood cells is needed, hydroxyurea may be useful. Central nervous system prophylaxis may be needed. Monitor laboratory results for tumor lysis syndrome and administer medications for prevention. Aggressive hydration may be administered.</td>
</tr>
<tr>
<td>Hyperleukocytosis</td>
<td>Headache, papilledema, altered level of consciousness, drowsiness, stupor, dizziness, visual disturbances, ataxia, coma, or sudden death</td>
<td>Vital signs and physical examination with special attention to neurologic assessment Complete blood and platelet count, CMP Neuroimaging</td>
<td>Control symptoms of nausea, vomiting, and cough, which may increase intracranial pressures; lumbar puncture is conducted after complete remission is attained; central nervous system prophylaxis (after complete remission) may be administered to patients who are high risk. Systemic treatment should be started. Elevate head of the bed. Interventions for potential aspiration and airway compromise include keeping suction equipment, oxygen setup, and airway at bedside.</td>
</tr>
<tr>
<td>Increased intracranial pressure (intracerebral leukocytosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ATRA**—all-trans retinoic acid; **CMP**—comprehensive metabolic panel; **D-dimer**—domain dimer; **DS**—differentiation syndrome; **HEENT**—head, eyes, ears, nose, throat; **msec**—milliseconds; **PT/INR**—prothrombin time/international normalized ratio; **PTT**—partial thromboplastin time

*Note. Based on information from Ahmed et al., 2007; Cephalon, Inc., 2008; Ezzone, 2006; Gucalp & Dutcher, 2001; Krimmel, 2003; Majhail & Lichtin, 2004; McCraw, 2008; Patatanian & Thompson, 2008; Roche Laboratories, 2003; Sanz et al., 2004, 2005, 2009; Trice & Hochberg, 2008; Vahdet et al., 1994; Wilkinson, 2001; Zitella et al., 2009.*
resolving coagulopathy in an average of four days (range 1–11) (Fenaux et al., 1993). In some patients, the coagulopathy may worsen before it improves; therefore, frequent nursing assessments are imperative. Supportive care interventions are started immediately and include the administration of blood products, including fibrinogen and fresh frozen plasma along with platelets and red blood cells (Lo-Coco, Ammatuna, Montesinos, & Sanz, 2008). Fibrinolytic inhibitors rarely are used (McCraw, 2008). The goal is to keep the fibrinogen level over 150 mg/dl and the platelet count between 30–50 x 10^9/L. Blood products are continued until the patient has no evidence of coagulopathy (Lo-Coco et al., 2008).

### Differentiation Syndrome

Differentiation syndrome (DS) is a complex set of signs and symptoms that may develop in patients who receive ATRA or arsenic trioxide (Patatanian & Thompson, 2008). DS is a life-threatening complication of treatment. Patients who develop one or more symptoms unexplained by other causes require prompt and early intervention to avoid morbidity and mortality associated with DS. Signs and symptoms of DS include respiratory distress, unexplained fever, weight gain, elevated white blood cell counts, pulmonary edema, interstitial pulmonary infiltrates, pleural and/or pericardial effusions, hypotension, congestive heart failure, and renal impairment (Ahmed et al., 2007; Camacho et al., 2000; Patatanian & Thompson, 2008; Tallman et al., 2000). Patients also may develop leukocytosis during treatment. Frankel, Eardley, Lauwers, Weiss, and Warrell (1992) concluded that leukocytosis frequently occurred but did not always predict development of DS. Camacho et al. (2000) reported that patients were more likely to develop DS if they developed leukocytosis after treatment was started.

The incidence of DS varies throughout the literature. Several studies have reported DS in as many as 24%–26% of patients...
with APL (Montesinos et al., 2009; Tallman et al., 2000), usually occurring within 2–21 days of therapy initiation (Frankel et al., 1992). Although no clear etiology exists for the development of DS, several assumptions have been reported in the literature. Each process is described separately but may overlap and work to affect the overall process (Ahmed et al., 2007; Patatanian & Thompson, 2008).

One hypothesis for the etiology is that the drug-induced release of cytokines from maturing myeloid cells may cause capillary leak syndrome (Margolin et al., 1989). The release of cytokines would enhance the immune defenses, resulting in some of the symptoms often seen (e.g., fever or hypotension) (Banasik, 2010). Another hypothesis is the infiltration of the organs by migration of maturing leukocytes, resulting in organ dysfunction as described by Frankel et al. (1992). The cellular migration to the lungs could explain the respiratory distress, and the migration to the kidneys could explain the impaired renal function. Lastly, these agents may promote the attachment of leukocytes to the capillary endothelium, causing local inflammation (Larson, Brown, & Sklar, 1997).

Once a diagnosis of DS is suspected, treatment should begin immediately with dexamethasone (10 mg twice daily via IV injection) for at least three days (Frankel et al., 1992). Dexamethasone is continued until symptoms resolve. Depending on the severity, treatment with ATRA or arsenic trioxide should be interrupted (Ahmed et al., 2007; Patatanian & Thompson, 2008; Sanz et al., 2009). ATRA or arsenic trioxide therapy can usually be restarted in most cases once the symptoms have resolved. The dose that is resumed is at the discretion of the provider (Cephalon, Inc., 2008; Roche Laboratories, 2003).

**QT Interval Prolongation With the Use of Arsenic Trioxide**

Administration of arsenic trioxide often is associated with electrolyte abnormalities that can cause prolongation of the QT interval on an electrocardiogram (Cephalon, Inc., 2008). Other risk factors that may cause a prolonged QT interval include the concurrent use of other drugs that may cause QT prolongation or electrolyte abnormalities, and current and past medical history of cardiac disease such as congestive heart failure (Cephalon, Inc., 2008). This prolongation can lead to a fatal ventricular arrhythmia called torsade de pointes (Sanz et al., 2009; Wilkinson, 2001). Careful monitoring of electrolytes and electrocardiograms is strongly recommended during the entire course of arsenic trioxide administration (Cephalon, Inc., 2008). Electrocardiograms are performed pretreatment (baseline) and then weekly during treatment. If the QT interval is prolonged to more than 500 milliseconds (msec), arsenic trioxide is held until the interval is less than 460 msec. Renal function, ions, and electrolytes (i.e., potassium, magnesium, calcium, and creatinine) are monitored closely (twice weekly during induction and once weekly during consolidation) (Wilkes & Barton-Burke, 2008; Wilkinson, 2001). Potassium and magnesium should be replaced to maintain the serum potassium concentration above 4 mEq/dl and the serum magnesium concentration above 1.8 mg/dl (Cephalon, Inc., 2008; Sanz, et al., 2005, 2009; Wilkinson, 2001). Low serum concentrations of potassium and magnesium can result in cardiotoxicity (Wilkinson, 2001).

**Other Complications**

The complications of coagulopathy, DS, and QT prolongation are more commonly seen in patients diagnosed with APL compared with other types of leukemia. Additional potential complications of APL include infection, hyperleukocytosis, tumor lysis, and increased intracranial pressure. These complications are not unique to APL, but do create potential nursing complications (see Table 2).

**Prognosis**

Prognosis for APL has not always been favorable. Historically, the clinical management of the disease was difficult and unpredictable because of the onset of life-threatening bleeding disorders. Through several clinical trials, clinicians now have a better understanding of several prognostic factors that may contribute to a poor outcome, including older age, presenting with a high WBC count, increased blast count, abnormal levels of creatinine, and the presence of coagulopathy (de la Serna et al., 2008; Sanz et al., 2000). The prognostic indicators also may correlate with patient risk for early relapse, which may occur in as many as 12.4% of patients (Sanz et al., 2000).

With the introduction of ATRA in 1992, the outcome for patients with APL has dramatically improved. A once mostly fatal disease related to hemorrhaging is now a highly curable malignancy when early treatment with ATRA and chemotherapy are used. Studies indicate that a complete remission can be attained in 90%–95% of patients with the combined ATRA and chemotherapy treatment (Asou et al., 2007; Burnett et al., 1999; de la Serna et al., 2008; Fenaux et al., 1993, 1999; Sanz et al., 2004), although a few patients that receive treatment may still succumb to the disease. A large multicenter study (de la Serna et al., 2008) found the death rate in patients with APL to be around 9%, with attributing factors such as hemorrhage (5%), infection (2.3%), and DS (1.4%). Also, with the addition of ATRA to chemotherapy, significant results have been seen in relation to disease-free survival rates for APL, ranging from 68%–86% at six years in several multicenter trials (Asou et al., 2007; Sanz et al., 2004).

**Implications for Oncology Nurses**

Nurses providing the necessary supportive care for patients with APL are faced with many challenges. Nurses should not only understand the underlying disease process, but the treatment course as well. This will enable them to better educate their patients, administer treatment safely, manage and monitor for possible side effects, and provide support to the patient and family throughout care.

Additionally, oncology nurses who work directly with patients on a daily basis are in a position to make an impact in the care of patients with APL. Nurses can play a major role in identifying patients that may be experiencing one of the many unique complications that can occur during the treatment course and help to identify any adverse effects of the drugs used during treatment. This article provides nursing implications as they relate to clinical presentation, treatment...
<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE</th>
<th>LABORATORY EFFECTS</th>
<th>COMMON SIDE EFFECTS</th>
<th>NURSING IMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic trioxide</td>
<td>IV</td>
<td>Increased AST and ALT</td>
<td>Increased AST and ALT</td>
<td>Assessment: History and physical assessment should include attention to kidney function, symptoms of differentiation syndrome, other drugs that may cause prolonged QT interval or electrolyte abnormalities, and signs and symptoms of peripheral neuropathy. Laboratory tests: Induction, at least twice weekly, if not more frequently, for complete blood count, electrolytes, kidney and liver function, and coagulation For consolidation, the same studies can be changed to weekly (monitor more frequently if abnormal). Monitor: Electrocardiogram at baseline and at least weekly to monitor for QT prolongation Correct QT interval that is greater than 500 msec (monitor more frequently if abnormal).</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>IV, intramuscular, intrathecal, subcutaneous</td>
<td>Decreased white blood cells, platelets, and hematocrit</td>
<td>Myelosuppression, hepatic abnormalities, fever, nausea, vomiting, diarrhea, mucositis, respiratory distress, pulmonary edema, tearing, ocular pain, and photosensitivity alopecia</td>
<td>Assessment: History and physical assessment should include attention to neurologic examination for signs and symptoms of mental status changes and confusion, mucositis, skin changes, and respiratory changes. Laboratory tests: Baseline complete blood count, electrolytes, kidney function, and liver function Monitor for: Cerebral toxicity, ocular side effects, and fever Special considerations: Corticosteroid eye drops with high-dose therapy</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>IV</td>
<td>Increased bilirubin, AST, alkaline phosphatase, and uric acid with tumor lysis</td>
<td>Myelosuppression, nausea, vomiting, diarrhea, stomatitis, fatigue, discoloration of urine for 24 hours, alopecia, and cardiac toxicity</td>
<td>Assessment: History and physical assessment should include attention to cardiac examination, skin and nail beds for hyperpigmentation, bowel pattern, mucositis, and fatigue. Laboratory tests: Complete blood count, electrolytes, kidney, and liver function studies Monitor with: Electrocardiogram at baseline, cardiac function, and extravasation Special considerations: Reduce dose for abnormal liver function studies; dose limit is 550 mg/m².</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>IV</td>
<td>Decreased white blood cells, platelets, and hematocrit</td>
<td>Myelosuppression, nausea, vomiting, diarrhea, alopecia, cardiac arrhythmias, hot flashes, rash, fever, lethargy, and discoloration of urine for 24 hours</td>
<td>Assessment: History and physical assessment should include a cardiac and a skin and nail examination. Laboratory tests: Complete blood count, electrolytes, and kidney and liver function studies (with special attention to bilirubin level). Patients should have a baseline ECHO or MUGA with results available prior to drug administration. Monitor for: Extravasation and cardiac toxicity Special considerations: Drug is light-sensitive. Reduce dose for renal or liver abnormalities and elevated bilirubin levels. Delay treatment if severe mucositis is present. Baseline ECHO or MUGA</td>
</tr>
</tbody>
</table>

ALT—alanine aminotransferase; AST—aspartate aminotransferase; ECHO—echocardiogram; msec—milliseconds; MUGA—multigated acquisition scan

Note. Based on information from Chan et al., 2007; Wilkes & Barton-Burke, 2008.
Table 3. Commonly Used Drugs in the Treatment of Acute Promyelocytic Leukemia (Continued)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE</th>
<th>LABORATORY EFFECTS</th>
<th>COMMON SIDE EFFECTS</th>
<th>NURSING IMPLICATIONS</th>
</tr>
</thead>
</table>
| Mercaptopurine      | Oral         | Decreased white blood cells, platelets, and hemoglobin and hematocrit               | Myelosuppression, hepatic toxicity, diarrhea, hyperpigmentation, mucositis, nausea, rash, stomatitis, and vomiting | Assessment: History and physical assessment should include attention to a history of gout, liver problems, dermatology issues, and nausea from certain medications.  
Laboratory tests: Complete blood count, electrolytes, kidney and liver function studies, uric acid levels at baseline and then monthly while on maintenance therapy.  
Monitor for: Compliance issues, any signs of gout, chronic nausea.  
Special considerations: Take on an empty stomach (one hour before or two hours after meals).  
Reduce dose for renal or liver abnormalities.  
Note. Based on information from Chan et al., 2007; Wilkes & Barton-Burke, 2008. |
| Methotrexate        | IV, intramuscular, intrathecal, oral | Decreased white blood cells, platelets, and hemoglobin and hematocrit               | Myelosuppression, nausea, vomiting, stomatitis, diarrhea, and rash; hepatotoxicity occurs more frequently with small doses; pulmonary toxicity may present as interstitial pneumonitis. | Assessment: History and physical assessment should include attention to a dermatology examination for a history of psoriasis, a history of rheumatoid arthritis, and a history of kidney or liver abnormalities.  
Laboratory tests: Complete blood count, electrolytes, kidney and liver function, and uric acid level  
Monitor for: Kidney or liver function abnormalities and myelosuppression.  
Special considerations: Drug should be stored at room temperature and protected from light.  
Avoid folic acid and its derivatives during therapy.  
Leucovorin rescue must be given with high doses.  
Awareness of drug interactions (very common)  
Reduce dose for renal or liver abnormalities.  
The patient should avoid nonsteroidal agents.  
Note. Based on information from Chan et al., 2007; Wilkes & Barton-Burke, 2008. |
| Mitoxantrone        | IV           | Decreased white blood cells, platelets, and hemoglobin and hematocrit and electrolytes | Myelosuppression, nausea, vomiting, stomatitis, diarrhea, rash, alopecia, and anorexia; cardiac toxicity (decreases left ventricular ejection fraction) and irreversible congestive heart failure can occur; discoloration of urine for 24 hours | Assessment: History and physical assessment should include attention to cardiac, hepatic, renal, gastrointestinal (bleeding or history of emesis with other chemotherapy) systems.  
Laboratory tests: Complete blood count, electrolyte, and kidney and liver function  
Monitor for: Myelosuppression before each dose, the need for an electrocardiogram before doses, respiratory or urinary tract infections, and pulmonary changes  
Special considerations: Baseline MUGA or ECHO before administration of drug  
Do not administer if absolute neutrophil count is less than 1,500 cells/mm³.  
Note. Based on information from Chan et al., 2007; Wilkes & Barton-Burke, 2008. |
| Tretinoin (all-trans-retinoic acid) | Oral         | Increased liver function and cholesterol and triglyceride levels                    | Differentiation syndrome, headache, fever, weakness, fatigue, edema, flushing, chest discomfort, depression, skin dryness, rash, pruritus, nausea, vomiting, diarrhea, mucositis, constipation, dyspepsia, upper respiratory tract disorders, and photosensitivity | Assessment: History and physical assessment should include attention to cardiac and pulmonary systems evaluating for differentiation syndrome and weight.  
Laboratory tests: Frequent monitoring of complete blood count (white blood cells), liver function, cholesterol, and triglyceride levels, as well as kidney function, prothrombin, and partial prothrombin.  
Monitor for: Abnormal laboratory results (liver, cholesterol, triglycerides, coagulation studies, and complete blood count), dehydration, and drug compliance.  
Special considerations: Take with food and avoid sun exposure.  
Note. Based on information from Chan et al., 2007; Wilkes & Barton-Burke, 2008. |

ALT—alanine aminotransferase; AST—aspartate aminotransferase; ECHO—echocardiogram; msec—milliseconds; MUGA—multigated acquisition scan
complications, and commonly used drugs in the treatment of APL (see Table 3). These nursing implications should guide oncology nurses in the delivery of safe and competent care for patients with APL.

Author Contact: Deborah Kirk Walker, DNP, FNP-BC, AOCN®, can be reached at dkirk2332@hotmail.com, with copy to editor at CJONEditor@ons.org.

References


