Acute Myeloid Leukemia: Advanced Practice Management From Presentation to Cure

MEREDITH BEATON, RN, MSN, AG-ACNP, GLEN J. PETERSON, RN, DNP, ACNP, and KELLY O'BRIEN, RN, MSN, ANP-C, ACNP-BC

From University of Colorado, Denver, Colorado

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Meredith Beaton, RN, MSN, AG-ACNP, 1665 Aurora Court, Aurora, Colorado 80045.

E-mail: meredith.beaton@cuanschutz.edu

Abstract

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, diagnosed in approximately 21,450 individuals annually in the US with nearly 11,000 deaths attributable to this disease (National Cancer Institute, 2020). Acute myeloid leukemia is a disease of the elderly, with the average age of diagnosis being 68 years old (Kouchkovsky & Abdul-Hay, 2016). It is a heterogeneous disease with widely varying presentations but universally carries a poor prognosis in the majority of those affected. Unfortunately, the 5-year overall survival rate remains poor, at less than 5% in patients over 65 years of age (Thein, Ershler, Jemal, Yates, & Baer, 2013). The landscape of AML is beginning to change, however, as new and improved treatments are emerging. Advanced practitioners (APs) are often involved in the care of these complex patients from the time of initial symptoms through diagnosis, treatment, and potentially curative therapy. It is vitally important for APs to understand and be aware of the various presentations, initial management strategies, diagnostic workup, and treatment options for patients with AML, especially in the elderly population, which until recently had few treatment options. This Grand Rounds article highlights the common presenting signs and symptoms of patients with AML in the hospital, including a discussion of the upfront clinical stability issues, oncologic emergencies, diagnostic evaluation, and current treatment options for elderly patients and those with poor performance status.

CASE STUDY

This patient case is fictional and does not represent events from an actual patient. The authors developed this fictional case for educational purposes only.

Thomas, a 62-year-old Caucasian male, was brought to the emergency department (ED) by his wife with severe shortness of breath, drowsiness, confusion, and hemoptysis. He had no significant past medi-

cal or surgical history, was not currently on medication, did not smoke or drink alcohol, and recently retired from an engineering firm. He has one sister, three children with his wife of 35 years, and no family history of cancer. He had a persistent sinus infection over the past 4 weeks that did not respond to several courses of antibiotics. On presentation to the ED, his vital signs were abnormal, with a fever of 102°F, heart rate of 126, respiratory rate of 30, blood pressure of 92/50, and oxygen saturation of 82% on room air, which improved to 92% on 4 L/min oxygen. He was ill-appearing, in moderate acute distress, oriented × 3, lethargic, pale, tachypneic with coarse lung sounds, with splenomegaly three centimeters below the left costal margin and 1+ bilateral lower extremity

edema. He had notable gingival hyperplasia and gum bleeding, lower extremity petechiae, and scattered ecchymoses.

His labs were notable for a white blood cell (WBC) count of 146×10^9/L with 80% peripheral blasts, excessive monocytes, hemoglobin 4.2 g/dL, platelets 9×10^9/L, international normalized ratio 2.2, fibrinogen 96 mg/dL, serum creatinine 1.9 mg/dL, blood urea nitrogen 38 mg/dL, potassium 4.9 mmol/L, uric acid 19 mg/dL, phosphorus 8.2 mg/dL, lactate dehydrogenase 1,100 U/L, sodium 129 mmol/L, and lactate 3.9 mmol/L. A chest x-ray was completed and showed a right lower lobe consolidation and small bilateral pleural effusions. An abdominal ultrasound showed an enlarged liver and spleen, and a CT brain was negative for acute hemorrhage.

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, diagnosed in approximately 21,450 individuals in the United States, with nearly 11,000 deaths attributable to this disease annually (National Cancer Institute, 2020). Acute myeloid leukemia is a disease of the elderly, with the average age of diagnosis being 68 years old (Kouchkovsky & Abdul-Hay, 2016). It is a heterogeneous disease with widely varying presentations, but the typical presenting constellation of symptoms includes fatigue, weight loss, and anorexia (Kouchkovsky & Abdul-Hay, 2016). Acute myeloid leukemia universally carries a poor prognosis in the majority of those affected. Unfortunately, the 5-year overall survival rate is poor, at less than 5% in elderly patients (> 65 years old; Thein et al., 2013). The landscape of AML is beginning to change, however, as new treatments are emerging. Advanced practitioners (APs) are integral in the care of these complex patients from the time of initial presentation through diagnosis, treatment, and potentially, cure. It is vitally important for APs to understand the diagnostic criteria and management strategies to improve outcomes and quality of life for patients with AML.

PATHOPHYSIOLOGY AND DIAGNOSIS
Acute myeloid leukemia is a hematologic disorder resulting from chromosomal translocations

and rearrangements resulting in the uncontrolled proliferation of myeloid blast cells and impaired production of normal thrombocytes, erythrocytes, and leukocytes (Kouchkovsky & Abdul-Hay, 2016). Initial diagnostic workup includes peripheral blood laboratory and bone marrow testing (Table 1) in order to determine the most appropriate therapy for the patient. Treatment options are dictated by the chromosomal mutations and translocations identified during diagnosis (Kouchkovsky & Abdul-Hay, 2016). Multiple molecular abnormalities are implicated as favorable, intermediate, or adverse variables (Table 2) pertaining to AML outcomes and should be assessed at the time of diagnosis and in the face of relapse (Marando & Huntly, 2020).

Case Study Continued
The hematology-oncology team was notified for continued management of Thomas' acute leukemia, and the medical intensive care unit (MICU) was consulted for management of his septic shock and acute hypoxic respiratory failure. Peripheral bloodwork was sent and a bone marrow biopsy was completed (Figure 1) confirming the diagnosis of AML with monocytic differentiation, and Thomas was found to be *FLT3* positive with complex karyotype, which is considered an adverse risk classification (Table 2) based on European LeukemiaNet risk stratification (Dohner et al., 2017).

Table 1. Diagnostic Testing in AML

Peripheral blood laboratory testing (Dohner et al., 2017)	• CBC with manual differential • Comprehensive metabolic panel, magnesium, phosphorus • Lactate dehydrogenase • Uric acid • Type and screen • PTT, PT/INR • D-dimer, fibrinogen • HIV • Acute hepatitis panel • Urine pregnancy test if patient is a child-bearing–aged female • Flow cytometry • Cytogenetic and molecular testing if bone marrow biopsy not feasible or was suboptimal • Urgent testing for APL if APL suspected, such as presence of DIC, with STAT FISH testing for t(15;17)
Bone marrow testing (Dohner et al., 2017; Ilyas et al., 2015)	• Morphology • Flow cytometry • Metaphase cytogenetics • FISH for AML panel • Molecular: Next-generation myeloid sequencing panel; IDH1/2 sequencing if patient is candidate for induction + IDH inhibitor clinical trial; FLT3 PCR
Other baseline/ diagnostic tests/ procedures	• Fingernails for next-generation myeloid sequencing panel • Central line placement (PICC preferred) • Echocardiogram in patients greater than 50 years of age, patients with a history or signs/symptoms of cardiac disease, or patients with prior exposure to cardiotoxic drugs or radiation • CT scan of neck, chest, abdomen, and pelvis if lymphadenopathy noted on physical exam • Lumbar puncture with intrathecal chemotherapy administration after aplasia achieved with no circulating blasts indicated for patients the following risk factors for CNS involvement: high WBC, CNS signs/symptoms, monocytic or myelomonocytic morphology (FAB M4/M5), CD56 expression, FLT3 positive, CD56 expression[a] • Oncofertility consultation in all male and child-bearing–aged females who wish to discuss options

Note. PTT = partial thromboplastin time; PT = prothrombin time; INR = international normalized ratio; APL = acute promyelocytic leukemia; DIC = disseminated intravascular coagulation; FISH = fluorescence in situ hybridization; AML = acute myeloid leukemia; PCR = polymerase chain reaction; PICC = peripherally inserted central catheter; CNS = central nervous system; WBC = white blood cells.
[a]Pratz & Levis (2017); Dohner et al. (2017).

CLINICAL STABILITY MANAGEMENT

Thomas presented with fever, evidence of bleeding, and electrolyte abnormalities. An infectious work-up was completed, and Thomas was given broad-spectrum antibiotics then transferred to the MICU for intubation and vasopressor support. His bleeding was managed with blood product transfusions and his electrolyte abnormalities were corrected.

Patients presenting with a new diagnosis of AML may have a variety of clinical syndromes ranging from mild to life-threatening, and initial management must focus on interventions to ensure clinical stability. Common complications include leukostasis, sepsis, tumor lysis syndrome (TLS), and disseminated intravascular coagulation (DIC). These four conditions require early detection and immediate management by the AP to reduce the chance of morbidity and mortality.

Leukostasis

Leukostasis is induced by high serum viscosity, therefore reducing blood flow contributing to tissue ischemia and infarct resulting in stroke-like symptoms, altered mental status, renal insufficiency, hypoxia, priapism, and/or extremity compartment syndrome. This most commonly occurs in patients with hyperleukocytosis (WBC count > 100×10^9/L) and monocytic differentiation (Giammarco et al., 2017). Patients with hyperleukocytosis are also at increased risk for TLS and DIC (Rollig & Ehninger, 2015). Not all patients with hyperleukocytosis experience signs and symptoms of leukostasis; however, those who develop symptoms must be treated immediately (Ganzel et al., 2012).

The management of leukostasis includes emergent initiation of leukapheresis, an apheresis procedure used to rapidly deplete leukocytes in the

Table 2. European LeukemiaNet Risk Stratification

Risk category	Genetic abnormalities
Favorable	• t(8;21)(q22;q22) • *RUNX1-RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22) • *CBF-MYH11* • Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low] • Biallelic mutated *CEBPA*
Intermediate	• Mutated *NPM1* and *FLT3*-ITD[high] • Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low] (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3) • *MLLT3-KMT2A* • Cytogenetic abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1) • *DEK-NUP214* • t(v;11q23.3) • *KMT2A* rearranged • t(9;22)(q34.1;q11.2) • *BCR-ABL1* • inv(3)(q21.3q26.2) or t(3;3) (q21.3;q26.2) • GATA2,MECOM(EVI1) • −5 or del(5q) • −7 • −17/abn(17p) • Complex karyotype • Monosomal karyotype • Wild-type *NPM1* and *FLT3*-ITD[high] • Mutated *RUNX1* • Mutated *ASXL1* • Mutated *TP53*

Note. Information from Dohner et al. (2017).

blood thus reducing stasis-related complications (Schwartz et al., 2013). Leukapheresis is associated with its own complications, including bleeding at the site of catheter placement, citrate-induced hypocalcemia, and bronchospasm (Faderl & Kantarjian, 2011). In addition to leukapheresis, patients are commonly treated with the leukocyte-reducing medication, hydroxyurea. Administration of hydroxyurea prior to intensive chemotherapy has been shown to improve outcomes in patients with hyperleukocytosis (Mamez et al., 2016). Although generally well-tolerated, hydroxyurea can cause severe cytopenias, mucositis, and cutaneous ulcerations. Labs every 6 to 12 hours is required to monitor the WBC count. Of note, leukapheresis is generally contraindicated in patients with acute promyelocytic leukemia (APL) as it may induce more severe DIC (Rollig & Ehninger, 2015).
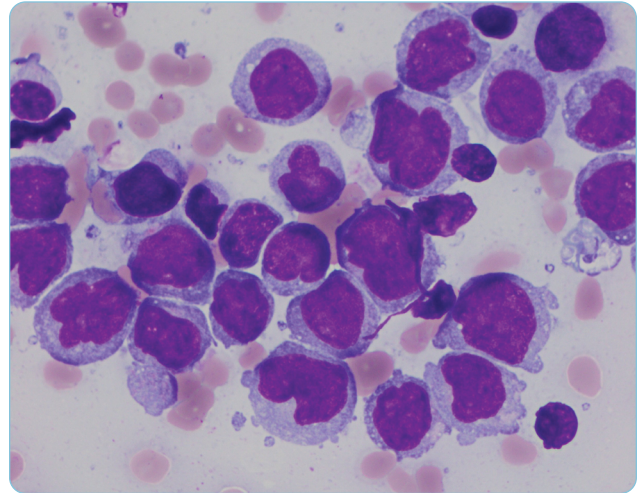

Figure 1. Thomas' bone marrow biopsy at 100× magnification: Abundant immature monocytoid cells (promonocytes and monoblasts) as well as myeloblasts completely replace the marrow.

Neutropenic Fever/Sepsis

Infection is the most common complication in patients with AML. Prophylaxis with broad spectrum antibacterial, antifungal, and antiviral agents is recommended during the neutropenic period (Freifeld et al., 2011; NCCN, 2019). All patients with acute leukemia should be considered functionally neutropenic and be treated aggressively when signs or symptoms of infection develop. Most newly diagnosed AML patients will develop fever during their course of treatment (Zimmer & Freifeld, 2016). Neutropenic fever is considered an oncologic emergency as it may rapidly progress to sepsis, shock, and death (Rhodes et al., 2017). It is important for APs to reliably identify and treat (Table 3) early signs of sepsis to reduce morbidity and mortality in these patients. Fever is an obvious sign of infection and may be the only sign in patients with AML (Zimmer & Freifeld, 2019). Other examples of early sepsis signs include chills, rigors, tachycardia, tachypnea, hypotension, lethargy or altered mental status, cool extremities, and decreased urination. Any combination of these clinical signs is concerning in patients with AML and extremely close monitoring and prompt intervention is required (Rhodes et al., 2017).

Tumor Lysis Syndrome

Tumor lysis syndrome is the most common complication in AML patients with a high burden of disease (high WBC count and blast percentage in

Table 3. Typical Initial Management of an AML Patient Who Develops a Neutropenic Fever or Other Signs of Infection

American Society of Clinical Oncology (ASCO) & Infectious Diseases Society of America (IDSA) Neutropenic Fever Management Guidelines
1. Vital signs assessment and intravenous fluid (IVF) administration if indicated.
2. Lab analysis and at least two sets of blood cultures (a set from each lumen of a central line if present and one peripheral set).
3. Initiation of monotherapy with a broad spectrum, antipseudomonal beta lactam antibiotic (within 1 hour of fever development). Vancomycin is also indicated in hemodynamic instability, radiographic pneumonia, skin or soft tissue infection, history of MRSA, or clinically evident central line infection.
4. Additional site-specific testing once antibiotics are initiated may include a chest x-ray, urinalysis, urine culture, and culture of other suspicious sites including stool and respiratory viral panel.

Note. MRSA = methicillin-resistant *Staphylococcus aureus*. Information from Freifeld et al. (2011); NCCN (2019); Rhodes et al. (2017); Taplitz et al. (2018).

a hypercellular marrow space; ONS, 2013). It is a complex metabolic oncologic emergency occurring after cellular destruction of rapidly growing tumor cells (Cairo & Bishop, 2004). This destruction, commonly induced by chemotherapy or other types of treatment, results in the release of intracellular components leading to hyperkalemia, hyperuricemia, and hyperphosphatemia with a secondary hypocalcemia due to phosphate binding. Tumor lysis syndrome can be classified as either laboratory TLS or clinical TLS based on the Cairo-Bishop classification (Table 4). These electrolyte abnormalities can lead to end-organ damage and ultimately death (McCurdy & Shanholtz, 2012). Complications related to TLS typically occur within the first several days of treatment, al-

Table 4. Cairo-Bishop TLS Syndrome Classification

Laboratory TLS	Clinical TLS
Uric acid ≥ 8.0 mg/dL (hyperuricemia)	Acute kidney injury defined as serum creatinine > 1.5 × the upper limit of normal for the patient's age and sex
Potassium ≥ 6.0 mEq/dL (hyperkalemia)	Cardiac arrhythmia or sudden cardiac death
Phosphorus ≥ 4.6 mg/dL (hyperphosphatemia)	Seizure, tetany, or other symptomatic hypocalcemia
Calcium ≤ 7.0 mg/dL (hypocalcemia)	Muscle cramps, tetany, hypotension, dysrhythmia, acute kidney injury

Note. Information from Cairo & Bishop (2004). TLS = tumor lysis syndrome. Patients must meet more than two of four laboratory criteria in the same 24-hour period within 3 days before or 7 days after initiation of chemotherapy.

though they can also occur prior to treatment due to cell turnover in patients with a high burden of disease (McCurdy & Shanholtz, 2012).

Patients at risk for TLS require close lab monitoring every 4 to 12 hours depending on the likelihood of developing TLS. All patients should receive IV hydration, allopurinol prophylaxis, and cautious electrolyte repletion with telemetry monitoring in high-risk patients (Cairo & Bishop, 2004; Williams & Killeen, 2019). Those who develop TLS should be treated aggressively to correct electrolyte abnormalities and manage end-organ damage. Consultation with the renal and intensive care teams is recommended in cases of grossly abnormal electrolytes, organ dysfunction, or high-risk patients who present with TLS (Mc-Curdy & Shanholtz, 2012). See Table 5 for detailed TLS management options.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation is commonly seen in newly diagnosed AML patients with increased risk in those with monocytic differentiation, hyperleukocytosis, and especially the APL subtype of AML. Disseminated intravascular coagulation is commonly caused by AML itself but can also present during infection. It is a metabolic oncologic emergency characterized by widespread intravascular thrombosis causing tissue ischemia, necrosis, and organ dysfunction (Levi & Skully, 2018). Conversely, DIC also causes a consumptive depletion of coagulant factors and platelets leading to hemorrhage (Levi & Skully, 2018). This combination of clotting and bleeding

may result in serious morbidity and mortality in patients with AML; therefore, immediate and aggressive management by the AP is key (Abedin & Altman, 2016).

The most important distinction for any new AML patient is to define whether the patient has APL. Prompt diagnostic testing (Table 2) in any AML patient exhibiting DIC is required to identify patients with this specific AML subtype. Patients with APL have an exceedingly high risk of DIC due to high expression of tissue factor, tumor necrosis factor, and interleukins, which increase clot risk (Abedin & Altman, 2016). Patients with APL may also develop phospholipid activation when exposed to anthracycline chemotherapy; therefore, the accuracy and timeliness of diagnosis prior to treatment are vitally important.

The management of DIC must focus on treating the underlying cause. Infectious complications should be treated appropriately; several options exist regarding disease treatment. The mainstay of DIC management is close laboratory monitoring every 4 to 12 hours and clinical monitoring for bleeding, blood product transfusion (Table 6), and supportive care to prevent and treat complications (Levi & Skully, 2018).

Case Study Continued

Thomas was started on hydroxyurea 2,000 mg three times daily and underwent leukapheresis immediately upon arrival in the MICU. He was extubated on day 2 of his admission and his pulmonary status returned to baseline. His electrolyte abnormalities were managed without the need for dialysis, and his renal function gradually returned to baseline. His DIC was supported with transfusions of blood products until treatment of his leukemia resulted in normalization of his labs and resolution of his bleeding.

TREATMENT

Before initiating treatment for patients with suspected AML, if a provider is suspicious that a patient may have APL, treatment with all-*trans* retinoic acid (ATRA) is indicated even before diagnosis is confirmed (Tallman & Altman, 2009). Once the diagnosis is confirmed, arsenic and potentially an anthracycline (for high-risk patients) have been shown to be highly effective in newly

Table 5. Standard Approaches to Electrolyte Aberrancies	
Electrolyte abnormality	**Interventions**
Hyperkalemia	- Avoid potassium supplementation - IV fluid infusion - Telemetry monitoring - Stabilize heart » Administer calcium gluconate - Shift potassium into cells » Administer sodium bicarbonate » Administer insulin/D50 » Administer albuterol - Remove potassium » Sodium polystyrene resin » Dialysis
Hyperuricemia	- Administer allopurinol (daily) - Administer rasburicase (by institutional guidelines) - Administer IVF infusion - Dialysis
Hyperphosphatemia	- Avoid phosphorus and calcium supplementation - Administer IVF - Administer phosphate binder (sevelamer, aluminum hydroxide, calcium acetate) - Dialysis
Hypocalcemia	If asymptomatic, no intervention; if symptomatic, administer calcium gluconate

diagnosed APL patients (Tallman & Altman, 2009). Patients undergoing treatment for APL require close monitoring as they may develop differentiation syndrome requiring administration of dexamethasone as well as the potential need for interruption of ATRA. Arsenic may cause QT prolongation necessitating frequent electrocardiogram monitoring and close electrolyte monitoring and replacements (NCCN, 2019).

Traditionally, treatment for AML, with the exclusion of APL as noted above, has included intensive chemotherapy followed by either allogeneic hematopoietic stem cell transplant (allo-SCT) or consolidation chemotherapy depending on risk stratification (Table 2). Ultimately, allo-SCT has been shown to provide the most antileukemic effects against AML, as demonstrated by the lowest rates of relapse in all clinical studies (Pagel, Gooley, Estey, Wood, & Appelbaum, 2008; Rowe & Tallman, 2010). Induction chemotherapy with cytarabine and an anthracycline, daunorubicin

Table 6. Disseminated Intravascular Coagulation Transfusion Management

Lab abnormality	Platelets < 30 × 10⁹/L (< 50 × 10⁹/L for active bleeding, presumed APL, active DIC)	INR > 1.9	Fibrinogen < 150 mg/dL
Blood product transfusion	Give 1 unit platelets	1–2 units FFP	1–2 units cryoprecipitate (preferred) or FFP

Note. Information from Ganzel et al. (2012). APL = acute promyelocytic leukemia; DIC = disseminated intravascular coagulation; INR = international normalized ratio; FFP = fresh frozen plasma.

and idarubicin having similar antileukemic effects, is considered standard of care for AML (Dombret & Gardin, 2016). Similarly, treatment with fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin has been shown to achieve remission and reduce risk of relapse in younger patients (Burnett et al., 2013). Potential side effects of induction chemotherapy include myelosuppression, infection (including sepsis), nausea, vomiting, diarrhea, mucositis, enterocolitis, transaminitis, hyperbilirubinemia, renal impairment, and cardiac complications including reduced ejection fraction post induction (Low et al., 2012). Targeted therapies can be incorporated into induction chemotherapy for specific genetic mutations such as midostaurin (Rydapt) or gilteritinib (Xospata), FLT3 inhibitors; gemtuzumab ozogamicin (Mylotarg), a CD33 antibody; ivosidenib (Tibsovo) and enasidenib (Idhifa), IDH1 and IDH2 inhibitors, respectively; and venetoclax (Venclexta), a BCL2 inhibitor.

The fact remains that elderly patients diagnosed with AML tend to do poorly and most intensive induction chemotherapy regimens are not recommended for older patients due to increased morbidity and mortality (Almeida & Ramos, 2016; Krug, Buchner, Berdel, & Muller-Tidow, 2011). Hypomethylators have traditionally been used as single-agent therapy for patients unfit for standard induction therapy but tend to have low response rates and are not curative (DiNardo et al., 2019). Common adverse effects of hypomethylators include cytopenias and neutropenic fever (DiNardo et al., 2019; NCCN, 2019). Additionally, hypomethylators can be used in conjunction with targeted therapies based on a patient's specific genetic profile with improved response rates (Almeida & Ramos, 2016). Most recently, there has been new research in the treatment of elderly adults with AML with venetoclax in combination with azacitidine or decitabine. In recent clinical trials, patients with poor-risk cytogenetics or elderly patients who did not qualify for induction chemotherapy had significantly improved remission rates as well as duration of remission and prolonged median overall survival rates when treated with venetoclax and azacitidine compared with standard treatment (DiNardo et al., 2019). Because of such promising data, our institution has recently started using venetoclax and azacitidine as front-line therapy for elderly patients with AML.

Advanced practitioners play a central role in the management of patients initiating treatment for AML. Complications associated with starting treatment are similar to those seen on initial presentation, including TLS, DIC, and sepsis. Additionally, the AP may be responsible for evaluating a patient's fitness for dose escalation of venetoclax during the first cycle. Similarly, APs may assist in evaluating the continuation of treatment prior to each new cycle of chemotherapy. The AP must know how to identify complications and when to hold therapy when complications arise. Some of the most common complications of venetoclax and azacitidine therapy include nausea, vomiting, constipation, neutropenic fever, fatigue, electrolyte imbalances, prolonged cytopenias, decreased appetite, cough, and peripheral edema (DiNardo et al., 2019).

Case Study Continued

Thomas' day 28 bone marrow biopsy showed a complete remission (CR). 2 weeks later he was readmitted for an allo-SCT with a myeloablative conditioning regimen. His post-transplant course was unremarkable and he was discharged on day +22 post allo-SCT. Thomas completed his day +80 bone marrow biopsy, which showed no evidence of disease and 100% donor chimerisms.

DISCUSSION

Acute myeloid leukemia is the most commonly occurring acute leukemia in adults, comprising approximately 80% of all adult leukemias (American Cancer Society, 2019). It remains a disease of the elderly, with the average age of diagnosis being 68 years old (American Cancer Society, 2019). Unfortunately, as many as 70% of elderly patients with AML will die from their disease within 1 year of diagnosis (Kouchkovsky & Abdul-Hay, 2016). Early recognition by APs of presenting symptoms, including life-threatening complications such as TLS, DIC, leukostasis, and sepsis, is important in reducing morbidity and mortality. Similarly, a thorough workup and identification of cytogenetic risk factors plays a critical role in determining treatment options for patients.

Until recently, intensive induction chemotherapy was the only option available for patients to achieve a possible cure. However, for elderly patients or those with comorbidities, induction chemotherapy significantly increases complications and treatment-related mortality (DiNardo et al., 2019). Only recently have low-intensity options such as venetoclax and azacitidine become available. This combination has significantly improved outcomes for older patients by achieving CR rates of 73% (DiNardo et al., 2019), allowing patients to proceed to transplant who otherwise would not have been able to. Because of these promising results, clinical trials have recently opened using venetoclax and azacitidine as frontline therapy for younger patients with newly diagnosed AML (ClinicalTrials.gov, 2018). Similarly to its use in the elderly population, venetoclax in combination with azacitidine offers fewer regimen-related side effects and lower morbidity and mortality for younger patients. Patients with AML, both young and old, may soon have the option to proceed to curative allo-SCT with significantly decreased pretransplant morbidity and mortality. Thus, it is critical that APs know how to recognize and manage newly diagnosed AML patients in order to decrease complications, improve overall survival, and help patients achieve better quality of life. ●

Disclosure

The authors have no conflict of interest to disclose.

References

Abedin, A., & Altman, J. K. (2016). Acute promyelocytic leukemia: Preventing early complications and late toxicities. *Hematology, American Society of Hematology Education Program, 2016*(1), 10–15. https://doi.org/10.1182/asheducation-2016.1.10

Almeida, A. M., & Ramos, F. (2016). Acute myeloid leukemia in the older adults. *Leukemia Research Reports, 6*, 1–7. https://doi.org/ 10.1016/j.lrr.2016.06.001

American Cancer Society. (2019). Cancer Facts & Figures 2019. Atlanta, GA.

Burnett, A. K., Russell, N. H., Hills, R. K., Hunter, A. E., Kjeldsen, L., Yin,...Milligan, D. (2013). Optimization of chemotherapy for younger patients with acute myeloid leukemia: Results of the medical research council AML15 trial. *Journal of Clinical Oncology, 31*(27), 3360–3368. https://doi.org/10.1200/JCO.2012.47.4874

Cairo, M. S., & Bishop, M. (2004). Tumour lysis syndrome: New therapeutic strategies and classification. *British Journal of Haematology, 127*(1), 3–11. https://doi.org/10.1111/j.1365-2141.2004.05094.x

ClinicalTrials.gov. (2018). Venetoclax and azacitidine for non-elderly adult patients with acute myeloid leukemia. Retrieved from https://clinicaltrials.gov/ct2/show/NCT03573024

DiNardo, C. D., Pratz, K., Pullarkat, V., Jonas, B. A., Arellano, M., Becker, P.S.,...Letai, A. (2019). Venetoclax combined with decitabine or azacitadine in treatment-naïve, elderly patients with acute myeloid leukemia. *Blood, 133*(1), 7–17. https://doi.org/10.1182/blood-2018-08-868752

Dohner, H., Estay, E., Grimwade, D., Amadori, S., Appelbaum, F. R., Buchner, T.,...Bloomfield, C. D. (2017). Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood, 129*(4), 424–447. https://doi.org/10.1182/blood-2016-08-733196

Dombret, H., & Gardin, C. (2016). An update in current treatments for acute myeloid leukemia. *Blood, 127*(1), 53–61. https://doi.org/10.1182/blood-2015-08-604520

Faderl, S., & Kantarjian, H. (2011). Leukemias: Principles and practice of therapy. https://doi.org/10.1002/9781444327359

Freifeld, A. G., Bow, E. J., Sepkowitz, K. A., Boeckh, M. J., Ito, J. I., Mullen, C. A.,...Wingard, J. R. (2011). Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases, 52*(4), e56–e93. https://doi.org/10.1093/cid/ciq147

Ganzel, C., Becker, J., Mintz, P. D., Lazarus, H. M. & Rowe, J. M. (2012). Hyperleukocytosis, leukostasis and leukapheresis: Practice management. *Blood Reviews, 26*(3), 117–122. https://doi.org/10.1016/j.blre.2012.01.003

Giammarco, S., Chiusolo, P., Piccirillo, N., Di Giovanni, A., Metafuni, E., Laurenti, L.,...Pagano, L. (2017). Hyperleukocytosis and leukostasis: Management of a medical emergency. *Expert Review of Hematology, 10*(2), 147–154. https://doi.org/10.1080/17474086.2017.1270754

Ilyas, A.M., Ahmad, S., Faheem, M., Naseer, M.I., Kumosani, T.A., Al-Qahtani, M.H., Gari, M. & Ahmad, M. (2015). Next generation sequencing of acute myeloid leukemia: Influencing prognosis. *BMC Genomics, 16*(1), S5. https://doi.org/10.1080/17474086.2017.1270754

Kouchkovsky, I. D., & Abdul-Hay, M. (2016). Acute myeloid

leukemia: A comprehensive review and 2016 update. *Blood, 6*(7), e441. https://doi.org/10.1038/bcj.2016.50

Krug, U., Buchner, T., Berdel, W. E., & Muller-Tidow, C. (2011). The treatment of elderly patients with acute myeloid leukemia. *Deutsches Arzteblatt International, 108*(51–52), 863–870. https://doi.org/10.3238/arztebl.2011.0863

Levi, M., & Skully, M. (2018). How I treat disseminated intravascular coagulation. *Blood, 131*(8), 845–854. https://doi.org/10.1182/blood-2017-10-804096

Low, M., Lee, D., Coutsouvelis, J., Patil, S., Opat, S., Walker, P.,...Wei, A. (2012). High-dose cytarabine (24 g/m²) in combination with idarubicin (HiDAC-3) results in high first-cycle response with limited gastrointestinal toxicity in adult acute myeloid leukaemia. *Internal Medicine Journal, 43*(3), 294–297. https://doi.org/10.1111/j.1445-5994.2012.02868.x

Mamez, A., Raffoux, E., Chevret, S., Lemiale, V., Boissel, N., Canet, E.,...Lengline, E. (2016). Pretreatment with oral hydroxyurea prior to intensive chemotherapy improves early survival of patients with high hyperleukocytosis in acute myeloid leukemia. *Leukemia & Lymphoma, 57*(10), 2281–2288. https://doi.org/10.3109/10428194.2016.1142083

Marando, L., & Huntly, B. (2020). Molecular landscape of acute myeloid leukemia: Prognostic and therapeutic implications. *Current Oncology Reports, 22,* Article number: 61. https://doi.org/10.1007/s11912-020-00918-7

McCurdy, M. T., & Shanholtz, C. B. (2012). Oncologic emergencies. *Critical Care Medicine, 40*(7), 2212–2222. https://doi.org/10.1007/s11912-020-00918-7

National Cancer Institute. (2020). SEER Cancer Stat Facts: Acute Myeloid Leukemia. Retrieved from https://seer.cancer.gov/statfacts/html/amyl.html

National Comprehensive Cancer Network. (2019). NCCN Clinical Practice Guidelines in Oncology: Prevention and treatment of cancer-related infections. V1.2019. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf

Oncology Nursing Society. (2013). Understanding and managing oncologic emergencies: A resource for nurses. Retrieved from https://www.ons.org/books/understanding-and-managing-oncologic-emergencies-resource-nurses-third-edition

Pagel, J. M., Gooley, T., Estey, E., Wood, B., & Applebaum, F. R. (2008). Impact of pre-transplant minimal residual disease assessed by flow cytometry on outcome following myeloablative hematopoietic cell transplantation for patients with AML-CR1. *Blood, 112*(11), 3253. https://doi.org/10.1182/blood.V112.11.3253.3253

Pratz, K. W., & Levis, M. (2017). How I treat FLT3-mutated AML. *Blood, 129*(5), 565–571. https://doi.org/10.1182/blood-2016-09-693648

Rhodes, A., Evans, L. E., Alhazzani, W., Levy, M. M., Antonelli, M., Ferrer, R.,...Dellinger, R. P. (2017). Surviving sepsis campaign: International guidelines for management of sepsis and septic shock. *Intensive Care Medicine, 43*(3), 304–377. https://doi.org/10.1007/s00134-017-4683-6

Rollig, C. & Ehninger, G. (2015). How I treat hyperleukocytosis in acute myeloid leukemia. *Blood, 125*(21), 3246–3252. https://doi.org/10.1182/blood-2014-10-551507

Rowe, J. M., & Tallman, M. S. (2010). How I treat acute myeloid leukemia. *Blood, 116*(17), 3147–3156. https://doi.org/10.1182/blood-2010-05-260117

Schwartz, J., Winters, J. L., Padmanabhan, A., Balogun, R. A., Delaney, M., Linenberger, M. L.,...Shaz, B. H. (2013). Guidelines on the use of therapeutic apheresis in clinical practice: Evidence-based approach from the writing committee of the American Society for Apheresis: The sixth special issue. *Journal of Clinical Apheresis, 28*(3), 145–284. https://doi.org/10.1002/jca.21276

Tallman, M. S., & Altman, J. K. (2009). How I treat acute promyelocytic leukemia. *Blood, 114*(25), 5126–5135. https://doi.org/10.1182/blood-2009-07-216457

Taplitz, R. A., Kennedy, E. B., Bow, E. J., Crews, J., Cleason, C., Hawley, D. K.,...Flowers, C. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update (2018). *Journal of Clinical Oncology, 36*(14), 1443–1453. https://doi.org/10.1200/JCO.2017.77.6211

Thein, M. S., Ershler, W. B., Jemal, A., Yates, J. W., & Baer, M. R. (2013). Outcome of older patients with acute myeloid leukemia: An analysis of SEER data over three decades. *Cancer, 119*(15), 2720–2727. https://doi.org/10.1002/cncr.28129

Williams, S. M., & Killeen, A. A. (2019). Tumor lysis syndrome. *Archives of Pathology & Laboratory Medicine, 143*(3), 386–393. https://doi.org/10.5858/arpa.2017-0278-RS

Zimmer, A. J., & Freifeld, A. G. (2019). Optimal management of neutropenic fever in patients with cancer. *Journal of Oncology Practice, 15*(1), 19–24. https://doi.org/10.1200/JOP.18.00269

Zimmer, A. J., & Freifeld, A. G. (2016). When to use prophylactic antibiotics in neutropenic patients. *Oncology (Williston Park), 30*(9), 838–840, 846.