or known colonization with penicillin/cephalosporin-resistant pneumococci or methicillin-resistant *Staphylococcus aureus*. In special situations where decreased susceptibility to vancomycin, vancomycin-resistant organisms, or vancomycin toxicity is documented, other options including linezolid, daptomycin, and quinupristin/dalfopristin need to be considered.

Caspofungin (or a similar echinocandin), voriconazole, or liposomal amphotericin B should be considered for antifungal treatment if fever persists for 4–7 days following initiation of empiric antibiotic therapy. Amphotericin B has long been used for antifungal therapy. Although liposomal formulations have improved the toxicity profile of this agent, its use has been limited to situations with high risk of or documented mold infections. Caspofungin has been approved for empiric antifungal treatment. Voriconazole has also been shown to be equivalent in efficacy and less toxic than amphotericin B. Antibacterial and antifungal antibiotics should be continued until patients are no longer neutropenic, regardless of whether a specific source has been found for the fever.

Recombinant hematopoietic growth factors have been incorporated into clinical trials in AML. These trials have been designed to lower the infection rate after chemotherapy. Both G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF) have reduced the median time to neutrophil recovery. This accelerated rate of neutrophil recovery, however, has not generally translated into significant reductions in infection rates or shortened hospitalizations. In most randomized studies, both G-CSF and GM-CSF have failed to improve the CR rate, disease-free survival, or overall survival. Although receptors for both G-CSF and GM-CSF are present on AML blasts, therapeutic efficacy is neither enhanced nor inhibited by these agents. The use of growth factors as supportive care for AML patients is controversial. We favor their use in elderly patients with complicated courses, those receiving intensive postremission regimens, patients with uncontrolled infections, or those participating in clinical trials.

TREATMENT FOR REFRACTORY OR RELAPSED AML

With the 7 and 3 regimen, 65–75% of younger and 50–60% of older patients with primary AML achieve CR. Two-thirds achieve CR after a single course of therapy, and one-third require two courses. Of patients who do not achieve CR, approximately 50% have a drug-resistant leukemia, and 50% do not achieve CR because of fatal complications of bone marrow aplasia or impaired recovery of normal stem cells. Patients with refractory disease after induction should be considered for salvage treatments, preferentially on clinical trials, before receiving allogeneic HSCT usually administered in patients who achieve a disease-free status. Because these patients are usually not cured even if they achieve second CR with salvage chemotherapy, allogeneic HSCT is a necessary therapeutic step.

In patients who relapse after achieving CR, the length of first CR is predictive of response to salvage chemotherapy treatment; patients with longer first CR (>12 months) generally relapse with drug-sensitive disease and have a higher chance of attaining a CR, even with the same chemotherapeutic agents used for first remission induction. Whether initial CR was achieved with one or two courses of chemotherapy and the type of postremission therapy may also predict achievement of second CR. Similar to patients with refractory disease, patients with relapsed disease are rarely cured by the salvage chemotherapy treatments. Therefore, patients who eventually achieve a second CR and are eligible for allogeneic HSCT should be transplanted.

Because achievement of a second CR with routine salvage therapies is relatively uncommon, especially in patients who relapse rapidly after achievement of first CR (<12 months), these patients and those lacking HLA-compatible donors or who are not candidates for allogeneic HSCT should be considered for innovative approaches on clinical trials (Table 132-5). The discovery of novel gene mutations and mechanisms of leukemogenesis that might represent actionable therapeutic targets has prompted the development of new targeting agents. In addition to kinase inhibitors for *FLT3*- and *KIT*-mutated AML, other compounds targeting the aberrant activity of mutant proteins (e.g., IDH2 inhibitors) or biologic mechanisms deregulating epigenetics (e.g., histone deacetylase and DNA methyltransferase inhibitors), cell proliferation (e.g., farnesyl transferase inhibitors), protein synthesis (e.g., aminopeptide inhibitors) and folding (e.g., heat shock protein inhibitors), and ubiquitination, or with novel cytotoxic mechanisms (e.g., clofarabine, sapacitabine), are being tested in clinical trials. Furthermore, approaches with antibodies targeting commonly expressed leukemia blasts (e.g., CD33) or leukemia initiating cells (e.g., CD123) and immunomodulatory agents (e.g., lenalidomide) are also under investigation. Once these compounds have demonstrated safety and activity as single agents, investigation of combinations with other molecular targeting compounds and/or chemotherapy should be pursued.

TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA

APL is a highly curable subtype of AML, and approximately 85% of these patients achieve long-term survival with current approaches. APL has long been shown to be responsive to cytarabine and daunorubicin, but previously patients treated with these drugs alone frequently died from DIC induced by the release of granule components by the chemotherapy-treated leukemia cells. However, the prognosis of APL patients has changed dramatically from adverse to favorable with the introduction of tretinoin, an oral drug that induces the differentiation of leukemic cells bearing the t(15;17), where disruption of the *RARA* gene encoding a retinoid acid receptor occurs. Tretinoin decreases the frequency of DIC but produces another complication called the APL differentiation syndrome. Occurring within the first 3 weeks of treatment, it is characterized by fever, fluid retention, dyspnea, chest pain, pulmonary infiltrates, pleural and pericardial effusions, and hypoxemia. The syndrome is related to adhesion of differentiated neoplastic cells to the pulmonary vasculature endothelium. Glucocorticoids, chemotherapy, and/or supportive measures can be effective for management of the APL differentiation syndrome. Temporary discontinuation of tretinoin is necessary in cases of severe APL differentiation syndrome (i.e., patients developing renal failure or requiring admission to the intensive care unit due to respiratory distress). The mortality rate of this syndrome is about 10%.

Tretinoin (45 mg/m^2 per day orally until remission is documented) plus concurrent anthracycline-based (i.e., idarubicin or daunorubicin) chemotherapy appears to be among the most effective treatment for APL, leading to CR rates of 90–95%. The role of cytarabine in APL induction and consolidation is controversial. The addition of cytarabine, although not demonstrated to increase the CR rate, seemingly decreases the risk for relapse. Following achievement of CR, patients should receive at least two cycles of anthracycline-based chemotherapy.

Arsenic trioxide has significant antileukemic activity and is being explored as part of initial treatment in clinical trials of APL. In a randomized trial, arsenic trioxide improved outcome if used after achievement of CR and before consolidation therapy with anthracycline-based chemotherapy. Patients receiving arsenic trioxide are at risk of APL differentiation syndrome, especially when it is administered during induction or salvage treatment after disease relapse. In addition, arsenic trioxide may prolong the QT interval, increasing the risk of cardiac arrhythmias.

Given the progress made in APL resulting in high cure rates, in recent years the goal has been to identify patients with low risk of relapse (i.e., those presenting with a leukocyte count ≤10,000/μL) where attempts are being made to decrease the amount of therapy administered and to identify patients at greatest risk of relapse (i.e., those presenting with a leukocyte count ≥10,000/μL) where new approaches can be developed to increase cure. A study compared the gold standard (tretinoin plus chemotherapy) in newly diagnosed non-high-risk APL with a chemotherapy-free combination of tretinoin and arsenic trioxide. An equivalent outcome was demonstrated between the two arms, and the chemotherapy-free regimen will likely become a new standard for non-high-risk APL patients.