TABLE 132-5 SELECTED AGENTS UNDER STUDY FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA

Class of Drugs	Examples of Agents in Class
Inhibitors of Mutant proteins	
Tyrosine kinase inhibitors	Dasatinib, midostaurin, quizartinib, sorafenib
IDH2 mutation inhibitor	AG-221
Epigenetic Targeting Compounds	
Demethylating agents	S110 (decitabine dinucleotide), oral azacitidine
Histone deacetylase inhibitors	Suberoylanilide hydroxamic acid (SAHA), MS275, LBH589
Inhibitors of Cell Proliferation	
Cell cycle inhibitors	Flavopiridol, CYC202 (R-roscovitine), SNS-032
Farnesyl transferase inhibitors	R115777, SCH66336
Aurora inhibitors	AZD1152, MLN-8237, AT9283
Inhibitors of Protein Synthesis and Degradation	
Aminopeptide inhibitors	Tosedostat
HSP-90 antagonists	17-Allylaminogeldanamycin (17-AAG), DMAG, or derivatives
Nedd8 activating enzyme (NAE) inhibitors	MLN4924
Cytotoxic Compounds	
Nucleoside analogues	Clofarabine, troxacitabine, elacytarabine, sapacitabine
Compounds with Immuno-Mediated Mechanisms	
Antibodies	CSL362 (anti-CD123), anti-CD33 (SGN33), anti-KIR
Immunomodulatory	Lenalidomide, interleukin 2, histamine dihydrochloride

autologous HSCT (5% mortality rate), but the relapse rate is higher than with allogeneic HSCT, due to the absence of the graft-versus-leukemia (GVL) effect seen with allogeneic HSCT and possible contamination of the autologous stem cells with residual tumor cells.

Prognostic factors may ultimately help to select the appropriate postremission therapy in patients in first CR. Our approach includes allogeneic HSCT in first CR for patients without favorable cytogenetics or genotype (e.g., patients who do not have *CEBPA* biallelic mutations or *NPM1* mutations without *FLT3*-ITD) and/or with other poor risk factors (e.g., an antecedent hematologic disorder or failure to attain remission with a single induction course). If a suitable HLA donor does not exist, investigational therapeutic approaches are considered. Indeed, postremission therapy is also a setting for introduction of new agents (Table 132-5). Because *FLT3*-ITD can be targeted with emerging novel inhibitors, patients with this molecular abnormality should be considered for clinical trials with these agents whenever possible.

Patients with the favorable CBF AML [i.e., t(8;21), inv(16), or t(16;16)] are treated with repetitive doses of high-dose cytarabine, which offers a high frequency of cure without the morbidity of transplant. Among AML patients with t(8;21) and inv(16), those with *KIT* mutations, who have a worse prognosis, may be considered for novel investigational studies, including tyrosine kinase inhibitors. The inclusion of gemtuzumab ozogamicin in induction and consolidation chemotherapy-based treatment has been reported to be beneficial in this subset of patients.

For patients in morphologic CR, immunophenotyping to detect minute populations of blasts or sensitive molecular assays (e.g., reverse transcriptase polymerase chain reaction [RT-PCR]) to detect AML-associated molecular abnormalities (e.g., *NPM1* mutation, the CBF AML *RUNX1/RUNX1T1* and *CBFB/MYH11* transcripts, the APL *PML/RARA* transcript), and the less sensitive metaphase cytogenetics or interphase cytogenetics by fluorescence in situ hybridization (FISH) to detect AML-associated cytogenetic aberrations, can be performed to assess whether clinically meaningful minimal residual disease (MRD) is present at sequential time points during or after treatment. Detection of MRD may be a reliable discriminator between patients who will continue in CR and those who are destined to experience disease recurrence and therefore require early therapeutic intervention before clinical relapse occurs. Although assessment of MRD in bone marrow and/or blood during CR is routinely used in the clinic to anticipate clinical relapse and initiate timely salvage treatment for APL patients, for other cytogenetic and molecular subtypes of AML, this is an area of current investigation.

SUPPORTIVE CARE

Measures geared to supporting patients through several weeks of neutropenia and thrombocytopenia are critical to the success of AML therapy. Patients with AML should be treated in centers expert in providing supportive measures. Multilumen right atrial catheters should be inserted as soon as patients with newly diagnosed AML have been stabilized. They should be used thereafter for administration of intravenous medications and transfusions, as well as for blood drawing.

Adequate and prompt blood bank support is critical to therapy of AML. Platelet transfusions should be given as needed to maintain a platelet count ≥10,000/μL. The platelet count should be kept at higher levels in febrile patients and during episodes of active bleeding or DIC. Patients with poor posttransfusion platelet count increments may benefit from administration of platelets from HLA-matched donors. RBC transfusions should be administered to keep the hemoglobin level >80 g/L (8 g/dL) in the absence of active bleeding, DIC, or congestive heart failure, which require higher hemoglobin levels. Blood products leukodepleted by filtration should be used to avert or delay alloimmunization as well as febrile reactions. Blood products should also be irradiated to prevent transfusion-associated GVHD. Cytomegalovirus (CMV)-negative blood products should be used for CMV-seronegative patients who are potential candidates for allogeneic HSCT. Leukodepleted products are also effective for these patients if CMV-negative products are not available.

Neutropenia (neutrophils <500/μL or <1000/μL and predicted to decline to <500/μL over the next 48 h) can be part of the initial presentation and/or a side effect of the chemotherapy treatment in AML patients. Thus, infectious complications remain the major cause of morbidity and death during induction and postremission chemotherapy for AML. Antibacterial (i.e., quinolones) and antifungal (i.e., posaconazole) prophylaxis in the absence of fever is likely to be beneficial. For patients who are herpes simplex virus or varicella-zoster seropositive, antiviral prophylaxis should be initiated (e.g., acyclovir, valacyclovir).

Fever develops in most patients with AML, but infections are documented in only half of febrile patients. Early initiation of empirical broad-spectrum antibacterial and antifungal antibiotics has significantly reduced the number of patients dying of infectious complications (Chap. 104). An antibiotic regimen adequate to treat gram-negative organisms should be instituted at the onset of fever in a neutropenic patient after clinical evaluation, including a detailed physical examination with inspection of the indwelling catheter exit site and a perirectal examination, as well as procurement of cultures and radiographs aimed at documenting the source of fever. Specific antibiotic regimens should be based on antibiotic sensitivity data obtained from the institution at which the patient is being treated. Acceptable regimens for empiric antibiotic therapy include monotherapy with imipenem-cilastatin, meropenem, piperacillin/tazobactam, or an extended-spectrum antipseudomonal cephalosporin (cefepime or ceftazidime). The combination of an aminoglycoside with an antipseudomonal penicillin (e.g., piperacillin) or an aminoglycoside in combination with an extended-spectrum antipseudomonal cephalosporin should be considered in complicated or resistant cases. Aminoglycosides should be avoided if possible in patients with renal insufficiency. Empirical vancomycin should be added in neutropenic patients with catheter-related infections, blood cultures positive for gram-positive bacteria before final identification and susceptibility testing, hypotension or shock,