Diagnosis and Treatment of Adult Acute Myeloid Leukemia Other than Acute Promyelocytic Leukemia

20

Peter H. Wiernik

Introduction

Acute myeloid leukemia (AML) includes all acute leukemias characterized by cells of other than lymphoid origin. AML subgroups with special clinical features have been defined by morphologic, immunologic, cytogenetic, and molecular techniques as discussed in Chaps. 14, 15, and 16. All subtypes other than acute progranulocytic leukemia (APL) are discussed in this chapter and APL is discussed in Chap. 21.

From a patient management point of view, the most serious pathologic consequence of AML is usually pancytopenia, rather than the production of leukemic cells. Therefore, management of AML requires prophylaxis and treatment of life-threatening complications of the absence of normal blood elements as well as eradication of the neoplastic clone from which the leukemic cells are derived. Prevention and treatment of the challenges to health posed by pancytopenia are discussed in the section "Supportive Care." It will be evident from those chapters that the management of a patient with AML is complicated and must be provided by a coordinated team of healthcare professionals thoroughly versed in the clinical nuances and complications of the disease, treatment of the disease, and impact of this catastrophic illness on patient, family, and society if optimal results are to be achieved. Such care is usually available only at major institutions and it is strongly recommended that, in general, the patient with AML be referred to such an institution immediately after the diagnosis is made. Some patients may not wish to be treated with curative intent and therefore need not be referred.

P.H. Wiernik, M.D., D.hc., FASCO
Cancer Research Foundation, Chappaqua,
New York, NY 10514, USA
e-mail: pwiernik@aol.com

Clinical Features of AML at Presentation

AML is diagnosed primarily in adults, although it can occur at any age. The median age at diagnosis in most large series is in the fifth or sixth decade, and the sexes have an approximately equal incidence. There is usually only a vague history of lethargy or lassitude prior to diagnosis, but approximately one-fourth of patients present with a serious infection of soft tissue or the lower respiratory tract associated on occasion with septicemia. Most patients have petechiae as evidence of intracutaneous capillary bleeding, but rarely more serious bleeding may be present initially. Bleeding gums after teeth brushing lead to the diagnosis in some cases. Lymphadenopathy is unusual in AML and splenomegaly is found in less than 25% of patients. If hepatomegaly is present it is almost always due to a cause other than AML in a de novo patient. Gingival hypertrophy (Fig. 20.1) is found in approximately half of patients with acute monocytic (FAB M5) or myelomonocytic (FAB M4) subtypes of AML. M4 and M5 patients have the highest incidence of all forms of extramedullary infiltration including leukemia cutis, and central nervous system (CNS) disease [1]. In some series granulocytic sarcoma is more common in patients with the M2 subtype of AML who demonstrate the t(8;21) cytogenetic abnormality. Perirectal lesions such as fissures or abscesses [2] may be present initially or during severe granulocytopenia at any time, especially in patients with M4 and M5 subtypes. The FAB subtypes defined by morphology and histochemistry, and the distribution of the subtypes among patients with AML, are identified in Table 20.1. More recent classifications based on cytogenetics and molecular characteristics are shown in Tables 20.2 and 20.3.

An elevated white blood cell (WBC) count is found in approximately one-third of patients with AML at diagnosis, and an equal number of patients have a normal WBC count or leukopenia. Hyperleukocytosis (WBC count >100,000 cells/μL) is uncommon, but may require special therapeutic interventions when present (see text to come). Blast forms

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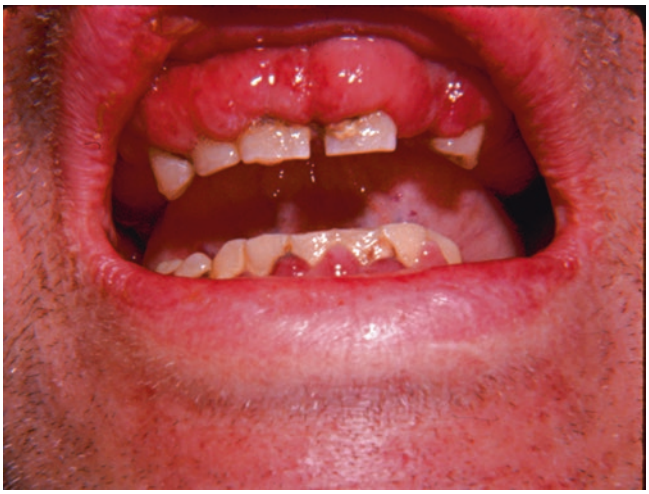

Fig. 20.1 Gingival hypertrophy in a patient with FAB M5 subtype of AML. Leukemic infiltration is the cause

Table 20.1 The French–American–British (FAB) Classification for AML

FAB type	Definition	% of adult AML patients
M0	Undifferentiated AML	5
M1	AML with minimal maturation	15
M2	AML with maturation	25
M3	Acute promyelocytic leukemia	10
M4	Acute myelomonocytic leukemia	20
M4E	Acute myelomonocytic leukemia with eosinophilia	5
M5	Acute monocytic leukemia	10
	(a) Monoblastic (b) Monocytic	
M6	Acute erythroid leukemia	5
M7	Acute megakaryocytic leukemia	5

Table 20.2 WHO Classification of AML with recurrent genetic abnormalities [3]

Karyotype abnormalities	Gene abnormalities
AML with t(8;21)(q22;q22)	RUNX1-RUNX1T1
AML with inv(16)(p13.1q(22) or t(16;16)(p13.1q22)	CBEB-MYH11
APL with t(15;17)(q22;q12)	PML-RARα
AML with t(9;11)(p22;q23)	MLLT3-KMT2A
AML with t(6;9)(p23;q34)	DEK-NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)	GATA2, MECOM
Acute megakaryoblastic leukemia with t(1;22)(p13.3;q13.3)	RBM15-MKL1
AML with	Mutated NPM1
AML with biallelic mutations of	CEBPA
Provisional: AML with	BCR-ABL1

Table 20.3 European LeukemiaNet Risk Stratification of AML [4, 5]

Risk groups	Included
Favorable	t(8;21); RUNX1-RUNX1T1
	Inv(16) or t(16;16); CBFB-MYH11
	Mutated NPM1 without FLT3-ITD and normal karyotype
	Biallelic mutated CEBPA and normal karyotype
Intermediate I	All cases with a normal karyotype except those in the favorable-risk group
	Wild-type NPM1 with or without FLT3-ITD
	Mutated NPM1 without FLT3-ITD
Intermediate II	t(9;11); KMT2A
	Cytogenetic abnormalities not favorable or adverse
Adverse	GATA2-MECOM (EVI1)
	T(6;9); DEK-NUP214
	T(v;11)(v;q23); KMT2A rearranged
	−5, or del 5(q); −7; abnl (17p)
	Complex karyotype without t(8;21), inv(16) or t(16;16), t(9;11) or other favorable abnormalities

are present in the peripheral blood of 85% of patients with AML before treatment. Therefore, about 15% of patients will not have a firm diagnosis made by examination of peripheral blood alone. The absolute granulocyte count is reduced in virtually all patients with AML and is less than 500 cells/ μL in approximately half of patients on the first examination. Thrombocytopenia is virtually universal and as many as one-third of patients will present with a platelet count <20,000/μL and they are candidates for immediate prophylactic platelet transfusion. Moderate anemia is the rule, but severe anemia may be found in patients with active bleeding other than petechial, or in patients in whom the diagnosis was delayed.

All patients with AML require bone marrow aspiration and biopsy. A biopsy is necessary to determine marrow cellularity. While the marrow is usually markedly hypercellular in de novo patients it may be hypocellular, especially in older patients, patients with secondary AML after treatment of another neoplasm with chemotherapy or radiotherapy, or patients who have developed AML after certain nonmalignant hematologic entities such as paroxysmal nocturnal hemoglobinuria [6]. Obviously, the marrow specimen must be obtained from a previously unirradiated site. It is important to assess marrow cellularity before and after treatment so that meaningful comparisons can be made. The pretreatment and subsequent marrow aspirates should be examined for morphology, histochemical reactions, immunophenotype, karyotype, and certain genetic mutations as discussed in this and other chapters in this section. Marrow aspirates submitted for immunological, cytogenetic, and molecular studies must be collected in heparin or acid citrate dextrose (ACD).

Leukemic blast cells account for at least one-half of marrow-nucleated elements in approximately 75% of AML patients at presentation. In elderly patients the leukemic cells may be less numerous. Usually, a diagnosis of AML is not made unless blasts account for at least 30% of the marrow white cells. Serial examinations in some patients will be necessary to determine the correct diagnosis and the rate of progression of the marrow infiltration. Rarely, the number of marrow blasts may increase slowly in some patients over several months or longer. It may be possible to withhold chemotherapy temporarily in some patients under those circumstances, especially elderly patients, as long as they are clinically well and the blood platelet and granulocyte counts are not dangerously low (<20,000/μL and <1000/μL, respectively).

The marrow aspirate may reveal other abnormalities in addition to leukemic cell infiltration. In patients with the M4 subtype relative erythroid hyperplasia is often present, despite anemia. There may be increased numbers of eosinophil precursors, especially in the M4E variant. Megakaryocytes are usually reduced in number except in secondary leukemia developing in a patient with polycythemia vera or primary thrombocytosis. Patients with the M7 subtype may have morphologically recognizable megakaryocytosis, but more often cell surface immunological or electron microscopic studies will be necessary to establish the lineage of the leukemic cells. Bone marrow necrosis may be evident prior to therapy [7], or discovered after therapy [8], especially in septic patients, and myelofibrosis may be detected in secondary leukemia or the FAB M7 subtype. Both marrow necrosis and myelofibrosis impair prognosis.

A minimal or moderate elevation in serum uric acid concentration is found in at least 50% of patients with AML. Serum lactate dehydrogenase levels may be elevated, especially in M4 or M5 subtypes, but usually to a lesser degree than in patients with acute lymphocytic leukemia (ALL). Lysozyme (muramidase) is elevated in the serum [9, 10] and urine of patients with M4 and M5 subtypes. As is the case with serum uric acid, levels of lysozyme directly reflect the body burden of tumor. Serial determinations of lysozyme may aid in evaluating response to therapy in patients with initial elevations [10].

AML is not simply a disease of the bone marrow and blood. Dysfunction of a number of organs may result directly from leukemic infiltration or indirectly from other consequences of the disease, and may dominate the clinical picture. Petechiae resulting from capillary hemorrhage secondary to thrombocytopenia are the most common skin and mucous membrane lesions. They tend to occur on dependent or traumatized areas of the body surface and may become confluent over some areas, especially in obese patients. Petechiae also occur on the surface and in the parenchyma of internal organs, but such lesions are usually clinically silent. Painless, nontender, small, raised nodules of leukemic cells may be palpable on the skin (leukemia cutis) of a small minority of patients with AML, especially those with M4 or M5 subtypes [11, 12], and approximately half of patients with leukemia cutis have an NPM1 mutation in their leukemia cells [13]. Such lesions are usually pink in color and not pruritic (Fig. 20.2). On rare occasion, leukemia cutis may be evident before bone marrow or other evidence of the disease is discovered [11], or it may be the first sign of relapse. Leukemia cutis has rarely been noted solely around central venous catheter exit sites or other injection sites [14, 15]. Leukemia cutis does not alter prognosis, but can be disturbing to the patient or even grossly disfiguring [16]. The lesions usually involve the entire corium, and the cells comprising them may have a different phenotype than the leukemic marrow cells [11]. The discordance may be due to partial differentiation of the skin lesion cells into macrophages [11].

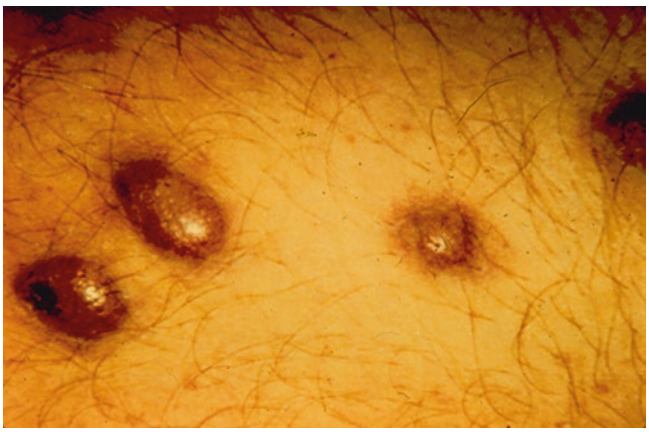

Fig. 20.2 Leukemia cutis in a patient with FAB M4 subtype of AML. The raised papules are due to leukemic infiltration of all layers of the corium

The lesions almost always respond to systemic chemotherapy rapidly, even if a complete remission is not ultimately obtained.

Rarely, a patient, especially a young patient, with AML will present with or develop a large subcutaneous or other mass of leukemic cells termed a granulocytic or myeloid sarcoma. On occasion, there is no other evidence of acute leukemia [17, 18]. Such lesions may also arise from subperiosteal areas of bone, particularly ribs, sternum, and orbit [19]. Granulocytic sarcoma of bone is rare, and other bone lesions such as radiographically seen metaphyseal lines that occur frequently in children with ALL are even rarer in adults.

Granulocytic sarcomas may occur in ovary [20], uterus [21], breast [22], cranial or spinal dura [23] (Fig. 20.3), and gastrointestinal tract [24] including liver [25], lung [26], mediastinum [27], prostate [28], and other organs and may present diagnostic difficulties in the absence of the usual

manifestations of AML [17, 29]. Such lesions may present as primary tumors of the organs involved, or suggest the diagnosis of lymphoma, plasmacytoma, or eosinophilic granuloma [30]. Typical AML may be discovered simultaneously, later, or never. A Wright-stained touch preparation of the lesion may help immeasurably in establishing the correct diagnosis. Immunohistochemical studies of fixed tissue may also be helpful in addition to routine histological studies [31, 32]. When isolated granulocytic sarcomas occur without other evidence of AML, radiotherapy [33] or surgery may be indicated. Although there is some evidence that treatment of an isolated granulocytic sarcoma with systemic chemotherapy will prevent the later occurrence of typical AML [34], this is not always the case and it is best to withhold systemic therapy until frank leukemia develops unless the granulocytic sarcoma cannot be treated locally.

Granulocytic sarcomas may occur more frequently in patients with M2 AML and t(8;21) [23, 35, 36], but it is clear that they also occur in patients with other cytogenetic abnormalities [37]. Their increased frequency as paraspinal tumors with t(8;21) may be related to the co-expression of a neural cell adhesion molecule (CD56) expressed by leukemic cells with that karyotype [38].

Acute febrile neutrophilic dermatosis (Sweet's syndrome) is a rare skin disorder that occurs in 1% of patients with AML for unknown reasons. It is more common in AML patients with FLT3 mutations [39]. The syndrome is characterized by fever, multiple painful papular and erythematous cutaneous eruptions, and a dense dermal infiltrate of mature granulocytes [40, 41]. A rapid response to glucocorticoids is usually obtained [42].

Fundic hemorrhage (Fig. 20.4) due to thrombocytopenia or leukemic infiltration of the retina may be found in patients of all ages with acute leukemia [43], including adults with AML [44].

Retinal leukemic infiltration is uncommon, is essentially confined to those patients with extreme hyperleukocytosis (blood blast count >200,000/μL), and is seen as one or more Roth-like spots with surrounding hemorrhage upon fundoscopic examination. Such lesions should be immediately irradiated if sight in the affected eye is to be preserved, but hemorrhage alone responds to successful platelet transfusion [44]. Other fundoscopic findings, such as cotton-wool spots; central vein obstruction; and vitreous, choroidal, or macular hemorrhage, are occasionally found [43, 44]. Certain treatments, such as high-dose cytarabine, may cause conjunctival and corneal pathology that results in impaired visual acuity [45]. The lesions resolve and normal visual acuity returns after discontinuation of the drug, and the problem can be prevented or attenuated with glucocorticoid ophthalmic drops administered during cytarabine treatment in most patients [46].

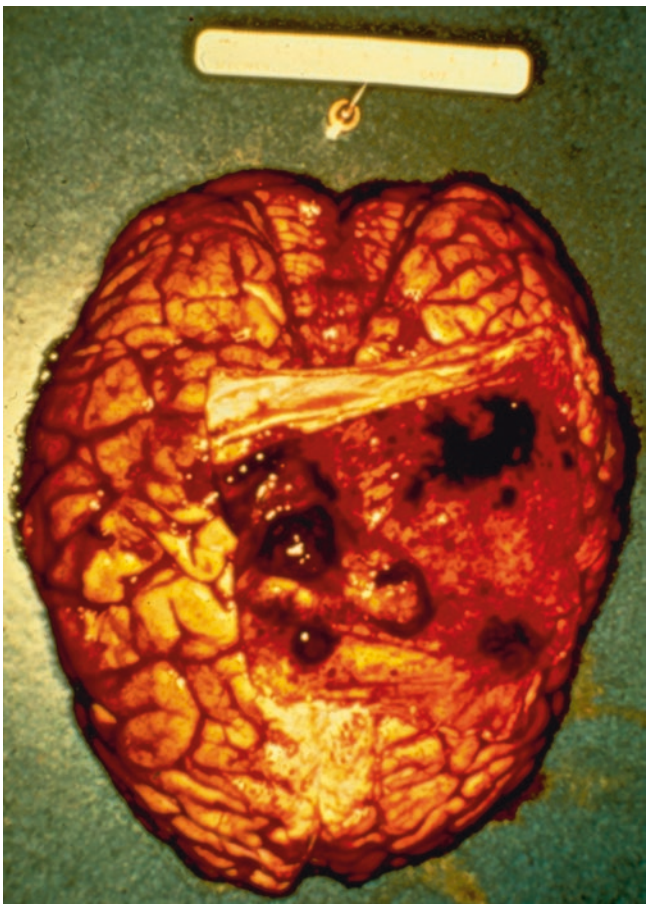

Fig. 20.3 A granulocytic sarcoma arising from the dura of the brain in a patient with FAB M2 subtype of AML with t(8;21) karyotype. The dura has been retracted to expose several dark nodules of tumor, which were *dark green*, due to myeloperoxidase contained in the cytoplasmic granules of the myeloid blast cells. The color fades when exposed to light

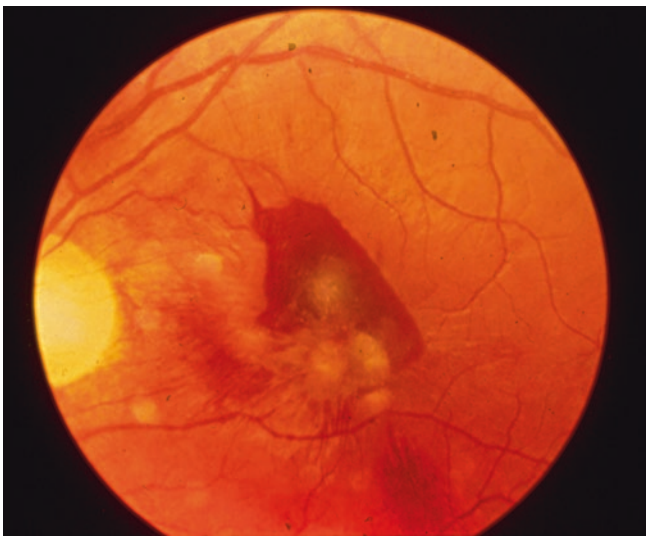

Fig. 20.4 Fundic hemorrhage in an AML patient with thrombocytopenia

Pulmonary dysfunction in patients with AML usually results from infection, which is discussed in Chaps. 53 and 54. A rare patient may develop dyspnea with or without an asthma-like syndrome due to pulmonary capillary leukostasis [47]. Such patients often have high blood blast counts [48, 49] and usually have the M3, M4, or M5 subtype of AML, but the frequency of this syndrome in patients with moderate degrees of leukocytosis may be underestimated [47]. The chest radiograph may be normal, show a ground-glass appearance suggestive of hemorrhage, or reveal diffuse alveolar consolidations [50]. This complication is frequently not recognized premortem, especially in patients with unrevealing chest radiographs [51]. Therefore, a therapeutic trial of bilateral low-dose whole-lung irradiation should be considered in an AML patient who has inexplicably developed progressively deteriorating pulmonary function [52–54]. A special form of this problem may occur after all-*trans* retinoic acid (ATRA) or arsenic trioxide therapy for acute promyelocytic leukemia and is fully discussed in Chap. 23. Severe and often fatal bilateral pulmonary hemorrhage may occur in end-stage patients who are thrombocytopenic and refractory to platelet transfusion, or in patients with a coagulopathy. This problem rarely arises during initial treatment. Although such hemorrhage has usually been ascribed to severe thrombocytopenia it may occur after successful platelet transfusion and other evidence suggests that its cause may be multifactorial. Diffuse alveolar cell damage may precede the hemorrhage, and cytoplasmic swelling and bleb formation have been noted in both capillary endothelial and alveolar lining cells in such patients [55]. While it is possible that these histologic changes represent toxic effects of extravascular blood, similar changes have resulted from cytarabine administration [56] or sepsis [57].

Heart conduction defects, murmurs, pericarditis, and congestive heart failure secondary to leukemic infiltration have been reported in AML [58–60]. Rarely, leukemic cardiac infiltration may occur in the absence of other evidence of AML [61]. These lesions are quite responsive to radiotherapy, which should be considered when leukemic infiltration of the heart cannot be ruled out [33].

It is important to have a dentist examine a patient with AML prior to therapy. Periodontal infections are common when AML is diagnosed and they may result in septicemia in a granulocytopenic patient. Dental extractions may be required [62] before initiation of chemotherapy, but often dental infections can be managed medically without interruption of leukemia treatment [63]. Other problems experienced by patients with AML in the region of the head and neck include leukemic infiltration of or hemorrhage into oropharyngeal structures that result in dysphagia or obstruction [64–66]. Leukemic infiltration of the inner, middle, and external ear has also been reported [67, 68].

As noted earlier, perirectal abscess and rectal fissure may develop in AML patients especially with the M4 or M5 FAB types. A small mucosal tear exquisitely painful on defecation or examination associated with fever may be the only indication of this potentially serious problem in a granulocytopenic patient, since infiltration and inflammation are often minimal [69]. Such lesions are usually the result of infection with gram-negative organisms, and bacteremia is frequent if proper treatment is delayed.

Necrotizing enterocolitis, or typhlitis, previously thought to occur primarily in children with acute leukemia, is described with increasing frequency in adults with AML who have been treated intensively [70]. Common symptoms include abdominal pain and distention with or without lower gastrointestinal bleeding. Abdominal radiographs may show only a nonspecific bowel gas pattern or lesions as serious as pneumatosis intestinalis, usually in the right colon. The lesions consist of mucosal ulcerations with inflammatory or leukemic infiltrates and usually involve the cecum but may also involve the ileum or the ascending colon. Bacteremia or fungemia frequently accompanies these lesions. Medical management may suffice [71], but surgery, which is usually successful when appropriate supportive care is available, may be required in some cases [72].

Renal dysfunction secondary to leukemic infiltration of the kidney or urate nephropathy is uncommon in adults with AML. Leukemic infiltration of the prostate [73] may obstruct the flow of urine and may rarely require irradiation. In most instances, however, induction chemotherapy will completely resolve the problem. Rarely, prostatic infiltration may be the first and only evidence of AML. Under no circumstances should a urinary catheter remain in place in a granulocytopenic AML patient.

Testicular relapse is common in ALL, especially in children, and has also been reported in adults with AML [74]. Postrelapse survival is frequently compromised in such patients.

Potassium wasting and other evidence of renal tubular dysfunction may occur in patients with the M4 and M5 subtypes who excrete lysozyme (muramidase), which is toxic to the proximal renal tubular epithelium [10]. The problem resolves with reduction of the tumor cell mass with chemotherapy. Lactic acidosis is a rare but difficult problem in AML [75]. Patients usually have large, vacuolated leukemic cells that may be difficult to accurately classify histologically. The etiology of the acidosis is obscure. Most patients have poorly controlled disease, and many have significant hepatic leukemic infiltration. The acidosis may require phenomenal quantities of alkali for control even after a partial remission of the leukemia is obtained.

Patients with AML may develop hypercalcemia [76], but hypocalcemia is more common. The latter may be a result of increased endogenous phosphorus production secondary to destruction of leukemic cells by either ineffective leukopoiesis, chemotherapy, or both, but septicemia and nephrotoxic antibiotics are frequently contributing factors [77]. On rare

occasion, hypocalcemia and hypophosphatemia may result from accelerated bone formation stimulated by leukemic cells [78].

Patients with AML subtypes M4 and M5 often present with hypocholesterolemia, which is thought to be due to increased low-density lipoprotein catabolism by mature monocytic phagocytes. Cholesterol levels return to normal with remission, and fall again with relapse of the leukemia [79].

Rarely, an AML patient presents with a markedly elevated peripheral blood blast cell count (>200,000 blasts/μL). This is a medical emergency since such a patient has approximately a 25% chance of a fatal intracerebral hemorrhage within a day or two [80–82]. This potential catastrophe is the result of intracerebral leukostasis secondary to increased blood viscosity. The hyperviscous blood causes sludging of blast cells at the low-pressure venous end of the capillary bed, which leads to plugging and eventual rupture of the vessel. The bleeding that then occurs would go unnoticed in most organs, but not in the brain. Those patients who undergo induction therapy with hyperleukocytosis are at risk for tumor lysis syndrome, which can be fatal even if recognized early [83]. Therefore, prophylactic emergency treatment directed at rapidly lowering the blood blast count and destroying established intracerebral foci of leukemic cells must be initiated at once (see discussion to come). A more common manifestation of CNS leukemia is meningeal infiltration with leukemia cells, which may arise from petechial hemorrhage in the meninges. Less than 2% of AML patients will have CNS leukemia at diagnosis. They are usually <45 years old, have a high WBC count of at least 50,000/μL, and have M4 or M5 FAB type (1). With proper treatment CNS leukemia at presentation does not impair prognosis. However, an isolated CNS relapse carries a poorer prognosis [1].

Many patients with AML are anergic to a battery of intradermal skin tests. This finding is of little clinical significance today since modern therapy has eliminated cutaneous anergy as a poor prognostic factor in AML. Some AML patients have decreased serum concentration of IgG and increased IgM concentration of unknown significance at presentation. Immunoglobulin levels usually normalize during induction therapy. On rare occasions, a serum paraprotein is present initially, which disappears after chemotherapy [84, 85]. Most patients with AML have a normal ability to raise a secondary antibody response [86, 87].

Diagnosis of AML

A thorough evaluation of a patient suspected of having AML must be conducted in a systematic fashion. A complete history should be taken with emphasis on exposure to medications, chemicals, and radiation, and the presence or absence of other diseases associated with an increased incidence of AML, including other neoplasms. A thorough family history should be taken, since a surprising number of patients with AML have a history of hematologic disorders in the family.

A complete physical examination is essential. If the patient is febrile, a thorough search for a focus of infection (periodontal disease, hemorrhoids, sinusitis, otitis, pharyngitis, pneumonia, abscess) must be made. The presence or absence of lymphadenopathy, splenomegaly, optic fundus pathology, CNS leukemia including cranial nerve palsy, and bleeding must be established. Granulocytopenic patients should not routinely undergo digital rectal examination.

Required peripheral blood studies include hematocrit, WBC count, platelet count, and differential WBC count. The peripheral blood smear should be examined by an oncologist or hematologist with experience in hematologic malignancies. A bone marrow biopsy and aspiration should be obtained from the posterior iliac crest with a Jamshidi needle or similar instrument. If it is impossible to obtain a posterior iliac crest aspirate, an attempt to obtain one from the sternum just under the ridge of the sternal angle with an Illinois or similar needle should be made. It is important to learn to perform these procedures properly from someone with experience. The biopsy is necessary to determine marrow cellularity and to assess the extent of the leukemic infiltrate. The aspirate should be examined after thin air-dried preparations are made, preferably on cover slips. No anticoagulant should be added to the aspirate obtained for routine staining and histochemistry, since some anticoagulants cause morphologic abnormalities in the leukemic cells, such as vacuolization, which may lead to diagnostic confusion. Aspirate smears should be stained with Wright's stain and a battery of histochemical reactions as detailed in Chap. 16. Such stains facilitate differentiation among the various AML subgroups, and between AML and ALL, and are required for proper French–American–British (FAB) classification. An iron stain should also be obtained on the biopsy to assess iron stores, and on the aspirate to identify sideroblasts often found in secondary AML, especially after treatment for Hodgkin's disease or multiple myeloma, and ringed sideroblasts that may be found in erythroleukemia (FAB M6).

An aspirate anticoagulated with heparin or ACD should be sent for immunophenotypic, cytogenetic, and molecular studies. The importance of these studies in the diagnosis of AML is detailed in Chaps. 17 and 18, and may give important prognostic information as discussed below.

Certain blood chemistry studies are required for proper assessment of the patient. Serum electrolytes, uric acid, lactate dehydrogenase, creatinine, lysozyme, and blood urea nitrogen should be determined. Routine coagulation studies and a plasma fibrinogen concentration are especially important in a patient suspected of having the M3 subtype of AML. Since hypogranular variants of that subtype exist, it is

important to study all patients initially. It should be remembered that some antibiotics commonly used in leukemia patients may cause abnormalities of coagulation unless vitamin K is administered prophylactically.

It is only necessary to examine the cerebrospinal fluid (CSF) routinely in asymptomatic AML patients with the M4 subtype. A lumbar puncture should only be performed in thrombocytopenic patients after a successful platelet transfusion has elevated the platelet count to 75,000/μL or more and in patients with a coagulopathy only after the plasma fibrinogen level has risen above 100 mg percent. Only 25-gauge needles should be used. The CSF obtained should be studied for routine parameters and, in addition, a cytocentrifuged specimen should be studied after staining with Wright's stain. Some training is required to accurately assess such specimens. Occasionally ependymal and other cells will be seen that may be mistaken for leukemic cells by the untrained observer. An elevated β_2-microglobulin CSF concentration may suggest occult CNS leukemia [88].

A posteroanterior and lateral chest radiograph should be obtained primarily as a baseline in an asymptomatic patient. Rarely, a mediastinal mass will be observed. This finding may confuse the observer unless one is aware of this rare manifestation of granulocytic sarcoma in AML [27].

Finally, the patient's blood should be typed and at least two packed red cell units cross matched with the patient's blood should be available at all times. If the patient has circulating lymphocytes the HLA type should be determined so that this information is available if bone marrow transplantation is contemplated in the future or if HLA-compatible platelet transfusions become necessary. At the same time, family members who agree to donate platelets, granulocytes, or bone marrow to the patient should also be HLA typed.

Preparation for Induction Therapy

It may not be necessary to begin induction chemotherapy immediately upon the diagnosis of AML. It is best to spend a day or two diagnosing the leukemic disorder precisely and resolving whatever medical emergencies are evident or developing.

Thrombocytopenic hemorrhage is more easily prevented than treated. Therefore, an AML patient with a platelet count less than 15,000–20,000/μL is a candidate for prophylactic platelet transfusion, which is discussed fully in Chap. 57. Prophylactic platelet transfusion has virtually eliminated hemorrhage as a cause of death during induction therapy. Platelet transfusion should not be given to a patient with a coagulopathy until low-dose heparin therapy is begun, or the coagulopathy may be aggravated.

An AML patient with a serious, uncontrolled infection at the time induction therapy is begun has a greatly reduced chance of remission. Therefore, documented or suspected infection should be under treatment and showing clear evidence of resolution before the institution of chemotherapy whenever possible. It is especially important not to begin chemotherapy until infection is controlled if the patient has circulating granulocytes. If absolute granulocytopenia exists in an infected patient, chemotherapy and antibacterial antibiotic therapy should be started simultaneously. Empiric broad-spectrum antibiotic therapy should be instituted immediately in a febrile granulocytopenic AML patient [89]. It should be remembered that fever may be the only clue to a serious infection in such a patient since the usual signs and symptoms of infection, which are largely due to granulocytic infiltration of infected tissues, may be absent [90]. Infection prevention and treatment for patients with AML are fully discussed in Chaps. 52 and 53, respectively.

The prophylaxis of intracerebral hemorrhage secondary to hyperleukocytosis [91] usually consists of emergency irradiation to the entire cranium with 600 cGy in a single dose and the administration of oral hydroxyurea (3 g/m^2 given daily for 2 days). The former will resolve already established intracerebral foci of leukemia, and the latter will rapidly reduce the blood blast count and thereby reduce blood viscosity, which is necessary to prevent reformation of intracapillary collections of blasts. Emergency leukapheresis has also been reported to be effective in this setting [92]. The procedure requires the availability of a blood cell separator and has not been demonstrated to be more effective than simple hydroxyurea administration. Management of hyperleukocytosis solely with hydration, urinary alkalinization, and allopurinol has been reported to be effective in infants [93] but is not recommended for adults.

Urate nephropathy is unusual in AML, except in patients with hyperleukocytosis or organomegaly due to leukemic infiltration. However, it is prudent to begin allopurinol (300 mg orally, daily for 1 or 2 days) before induction therapy and equally prudent to discontinue the drug after the marrow has become hypocellular following chemotherapy. Unnecessary prolongation of allopurinol administration may result in cutaneous eruption, which occurs with about 20% of prolonged courses of the agent or, on rare occasion, permanent marrow aplasia [94]. Patients who present with elevated serum uric acid concentration and an unusually large tumor load due to hyperleukocytosis or granulocytic sarcoma will require double or triple the usual allopurinol course initially, or treatment with recombinant urate oxidase (rasburicase) [95, 96].

Infection prevention methods should be instituted before induction therapy. The patient should be placed in strict reverse isolation in a meticulously cleaned room with air supplied only through high-efficiency particulate (HEPA) air filtration systems.

A triple-lumen Hickman catheter or similar device should be installed prior to treatment to facilitate blood drawing and intravenous therapy. If at all possible, the catheter should be placed at a time when the patient has circulating granulocytes, and use of the catheter should be restricted to personnel who have been specifically trained in the proper use and care of such devices.

Special consideration needs to be given to the pregnant patient with AML. Commonly administered induction agents other than idarubicin [97] can be given with relative safety to mother and fetus during the third and probably the second trimester [98–100] and should be given at doses based on actual body weight [101]. Children born to mothers undergoing induction therapy for AML during those trimesters have experienced only minor problems at birth and after long-term follow-up [98–102]. However, the use of lipophilic idarubicin during pregnancy may result in neutropenia and/or cardiac dysfunction in the neonate [97]. Induction therapy during the first trimester is very likely to result in abortion [99], and the diagnosis of AML itself in the first trimester may cause spontaneous pregnancy loss [101]. It may therefore be prudent to induce abortion under controlled circumstances in the first trimester. Rarely, spontaneous temporary remission of untreated AML may occur after cesarean section [22], or other event, usually a pyogenic infection [103].

Chemotherapy for AML

Chemotherapy for AML is administered in two stages: induction therapy followed by consolidation therapy. Allogeneic or autologous bone marrow transplantation may follow consolidation therapy in some circumstances, or consolidation therapy may be followed by or replaced by long-term maintenance therapy in other circumstances. The latter approach is not commonly used, although there is a rationale for it [104–106]. The purpose of induction therapy is to achieve complete clinical and hematological remission, which is defined as the absence of all clinical evidence of leukemia as well as a normocellular marrow devoid of leukemic cells and with normal trilineage hematopoiesis. Peripheral blood counts and differential WBC count are usually within the normal range in patients in complete remission, although in a minority of cases the platelet count may not recover to normal levels [107, 108]. Patients without complete platelet recovery may have impaired long-term survival compared with others [108, 109]. In patients whose AML is characterized by a specific gene mutation, quantitation of that mutation in marrow or peripheral blood cells [110] after complete hematologic remission is obtained may yield significant prognostic information with regard to the likelihood of relapse and even drive postremission therapy decisions. Such minimal residual disease testing is likely to become standard in the near future, once technical details are worked out [111–113]. The purpose of postremission therapy is to reduce the body burden of subclinical leukemia to, theoretically, zero. There is overwhelming evidence to support the concept of postremission therapy in that in virtually all studies in which outcome with and without postremission therapy has been prospectively compared, disease-free and overall survivals are greater in patients who continue treatment while in complete remission. Furthermore, most available data demonstrate a dose–response relationship for postremission therapy so that, in general, cure rates are higher with postremission dose-intense regimens than with regimens of lesser dose intensity. While there is no question that intensive postremission therapy is currently necessary in order to achieve optimal results, some studies have suggested that intensification of induction therapy may improve disease-free and overall survival despite no improvement in remission rate [114].

Although there is little evidence that the major FAB subtypes respond differently to standard induction therapy for AML, the development of ATRA therapy for the M3 subtype suggests that more subtype-specific therapy for AML may be developed in the future and that remission induction by mechanisms other than leukemia cell kill may be possible. There is already evidence that some dose-intense postremission regimens may be more beneficial in AML patients with favorable cytogenetics than in others [115].

There is no need for CNS prophylaxis in adult AML. The frequency of overt CNS leukemia is less than 1–2%, and cytarabine is virtually always used during induction therapy in intravenous doses that result in therapeutic CSF levels.

Results of induction therapy vary depending on a variety of prognostic factors. Patient age is the oldest recognized such factor. Patients over the age of 60–65 years have significantly lower complete response rates to induction therapy in most studies. Cytogenetic abnormalities are divided into favorable, intermediate, and unfavorable groups with respect to prognosis for complete response to therapy, and overall survival. The favorable group includes inv(16), t(8;21) without kit mutations, and t(15;17). A normal karyotype has an intermediate prognosis as does t(8;21) with kit mutation, and monosmy 5 or 7 (usually seen in secondary AML) as well as a complex karyotype have an unfavorable effect on prognosis [115]. See Tables 20.2 and 20.3.

More recently a number of genetic aberrations that affect prognosis in AML patients treated with currently available therapy have been identified [116]. In some instances, new treatments have been devised that partially offset the poor prognosis associated with some of these mutations. FLT3 mutation is one of the most common mutations seen in AML. The fems-like receptor tyrosine kinase (FLT3) expressed by immature

hematopoietic cells is important for the normal development of hematopoietic stem cells. Activating mutations caused by either an internal tandem duplication (ITD) or multiple amino acids in the juxtamembrane region or point mutation in the activation loop of the tyrosine kinase domain (TKD) are present in approximately 30% of patients with de novo AML. FLT3-ITD mutation is the most common molecular abnormality associated with adult AML. FLT3-ITD mutation occurs in patients with all FAB and cytogenetic designations, but is most common in patients with FAB M3. Such mutations have a negative impact on disease-free and overall survival in patients with a normal karyotype but have little influence on prognosis of patients with favorable or unfavorable cytogenetics. Recently developed inhibitors of these mutations given with standard induction therapy partially neutralize the activity of FLT3 mutations in the laboratory [117, 118] and partially negate the impaired prognosis conferred by these mutations in the clinic [119–121].

A number of other molecular prognostically significant factors have recently been identified, such as NPM1, CEBPA, IDH1, IDH2, and WT1 mutations, and they have the potential for becoming therapeutic targets in the future. NMP1 is frequently mutated in AML and preclinical studies suggest that cells with the mutation may undergo apoptosis with retinoic acid or arsenic trioxide treatment [122]. In a study of 148 AML patients 60 years old or older with normal cytogenetics, Becker et al. [123] reported that 56% of the patients had NPM1 mutations and those patients had a higher complete response rate [84% vs. 48% for patients without the mutation ($p < 0.001$)] as well as significantly longer disease-free and overall survival. The prognostic impact of the mutation was observed predominantly in patients at least 70 years old. Others have reported similar results [124]. See Table 20.4.

Damm et al. [125] found that patients with normal cytogenetics and a single-nucleotide polymorphism located in the mutational hot spot of the WT1 gene had improved relapse-free and overall survival compared with others, and Dufour et al. [126] reported that patients with normal karyotype biallelic CEBPA gene mutations, compared with those with monoallelic mutations or wild-type CEBPA, had significantly better overall survival after standard therapy. Conversely, Kornblau et al. [127] reported that highly phosphorylated Foxhead transcription factor (FOXO) in leukemic cells is a significant negative prognostic factor for survival in AML, independent of karyotype. Phosphorylated FOXO levels were higher in patients with FLT3 mutations, and were associated with higher WBC counts and a higher percent of blood and marrow blast cells.

In general, approximately 65–70% of unselected patients with de novo AML will achieve complete remission after one course of induction therapy. At least 30%, and perhaps as many as 40%, of complete responders will be cured after appropriate postremission therapy. In some studies long-term results are significantly better in women [128] and in virtually all studies they are better in patients <60 years old. Results of induction therapy are likely to improve as inhibitors of diver mutations are developed.

An excellent review of the molecular biology of AML has recently appeared [129].

Table 20.4 Examples of gene alterations affecting prognosis in AML [111, 129–135]

Gene	Prognostic effect	FAB type
FLT3-ITD	Poor with intermediate karyotype	
RUNX1	Poor	43% in M0
TP53	Poor-almost always with complex karyotype	36% in M6
FOXO phosphorylated	Poor	
EVI1	Poor	
IDH1, IDH2	Conflicting data	
DNMT3A	Poor if normal karyotype	26% in M2
KIT	Poor in CBF AML	
MLL-PTD	Poor	
TET2	Poor with intermediate karyotype	
TET2 hypomethylation	Very favorable	
NPM1	Favorable in FLT3-ITD mutation negative	42% in M1 57% in M4 49% in M5a 70% in M5b
CEBPA biallelic	Favorable	
WT1	Favorable if other than normal karyotype Unfavorable with normal karyotype	

PTD partial tandem duplication, *CBF* core-binding factor

Induction Therapy

The standard induction regimen for adults with AML for decades has been the two-drug combination of daunorubicin and cytarabine, and complete response rates on the order of 65% in unselected patients have regularly been reported with that combination [136–140] in unselected patients. Patients over the age of 60 years usually have a lower response rate. In a prospective, randomized ECOG study elderly patients treated with a standard induction regimen plus GM-CSF had a higher response rate, lower rate of infection, and lower death rate [141]. However, a similar study utilizing an investigational GM-CSF derived from *Escherichia coli* showed no advantage for the growth factor [142]. The ECOG study demonstrated that GM-CSF does not stimulate leukemia when used after marrow hypoplasia occurs, since patients receiving the growth factor did not have shorter disease-free or overall survival [141].

A commonly used induction regimen is a continuous intravenous 7-day infusion of cytarabine given at the rate of 100 mg/m^2 per day, plus daunorubicin given as 3 daily bolus injections of 45 mg/m^2 each, beginning on the first day of treatment. However, recent data suggest that much larger doses of daunorubicin may be more efficacious than standard doses. Fernandez et al. [143] randomly allocated 657 patients with previously untreated AML aged 17–60 years to cytarabine, 100 mg/m^2/day as a continuous 7-day I.V. infusion plus daunorubicin 45 mg/m^2 daily for 3 days or daunorubicin 90 mg/m^2 on the same schedule. The results were recently reported after more than 80-month median follow-up [144]. The higher daunorubicin dose resulted in a higher complete response rate (71% vs. 59%) and improved overall survival (median 25.4 months vs. 16.6 months, respectively). Only patients aged <50 years benefited from the high-dose therapy. The median overall survival with high-dose daunorubicin was 44.7 months compared with 20.7 months for the standard-dose patients younger than age 50. Patients with favorable cytogenetics benefited the most from the high-dose regimen but those with intermediate and unfavorable cytogenetics may have done so as well, but his could not be confirmed on univariate analysis. Patients with FLT3-ITD, NPM1, IDH, or DNMT3A mutations benefited as well from high-dose daunorubicin, and the high-dose induction regimen was required for the favorable impact of the NPM1 mutation on the disease to be evident. The rates of serious adverse events were similar in the two groups, but longer follow-up of survivors will be needed before that fact can be verified. Löwenberg et al. [145] conducted a similar study in older patients. They randomized 813 newly diagnosed AML or high-risk refractory anemia patients aged 60–83 years to receive daunorubicin at one of the two doses used in the Fernandez study [143] and cytarabine, 200 mg/m^2/day in a continuous 7-day infusion. The CR rate was 64% with the 90 mg/m^2 daunorubicin dose and 54% with the 45 mg/m^2 dose. Overall survival was similar in the two groups, but patients aged 60–65 years had greater event-free (29% vs. 14%) and overall (38% vs. 23%) survival with the 90 mg/m^2 dose of daunorubicin. A Korean study using the same regimens reported a higher complete response rate, and longer event-free and overall survival with similar toxicity in 383 patients ≤60 years old [146]. These three studies are interesting, but they need to be viewed critically. In many published studies the response rates with standard-dose daunorubicin are better than those reported in at least one of these studies [143] and similar to the results obtained with the daunorubicin 90 mg/m^2 dose. Patients who receive a total of 270 mg/m^2 daunorubicin with one course of the high-dose daunorubicin will probably not be able to receive retreatment in the future with an anthracycline should the need arise. Furthermore, the long-term toxicity of the high-dose daunorubicin regimen is unknown.

Burnett et al. [147] randomized 1206 patients, mostly younger than 60 years, with previously untreated AML or high-risk myelodysplastic syndrome to receive daunorubicin, 90 or 60 mg/m^2 on days 1, 3, and 5, combined with cytarabine, 100 mg/m^2/day as a 10-day continuous infusion. All patients received a second induction course with daunorubicin, 50 mg/m^2 on days 1, 3, and 5. There was no difference in complete response rate overall or 2-year overall survival in any subgroup. However, 60-day mortality was significantly increased in the patients who received daunorubicin, 90 mg/m^2. Although there are differences in the design of this study and the Fernandez study described above [143, 144] the results of the two studies are completely at odds with each other, especially with respect to toxicity of daunorubicin, 90 mg/m^2. Other smaller studies have addressed the question of daunorubicin dosage intensification. Prebet et al. [148] concluded from a retrospective study of AML newly diagnosed patients with core-binding factor that relapse-free survival was significantly better with daunorubicin 90 mg/m^2 than with daunorubicin 60 mg/m^2 and that there was a trend ($p = 0.07$) for a superior 2-year overall survival with the former. Another small retrospective study concluded that daunorubicin 90 mg/m^2 improved overall survival compared with daunorubicin 60 mg/m^2 [149]. Pautas et al. [150] compared daunorubicin 80 mg/m^2 daily for 3 days with idarubicin 12 mg/m^2 daily for 3 days or, in another group, daily for 4 days in 468 patients with ages ranging from 50 to 70 years. All patients received cytarabine as well. Both idarubicin schedules resulted in a significantly higher complete response rate than did daunorubicin, but there was no difference in relapse rate, event-free survival, or overall survival among the treatments.

From a meta-analysis of six randomized controlled trials Gong et al. [151] found significant improvement in complete response rate, event-free survival, and overall survival with daunorubicin 90 mg/m^2 compared with lower daunorubicin doses, but no differences in disease-free survival, relapse rate, or toxicity. Another meta-analysis found that both high-dose daunorubicin (90 mg/m^2 × 3 and 50 mg/m^2 × 5 studies lumped together) and idarubicin, 12 mg/m^2 × 3, achieve 5-year survival rates of 40–50% in patients ≤60 years of age [152]; another such study in adults showed that both high-dose daunorubicin and standard-dose idarubicin were superior to standard-dose daunorubicin in achieving complete response and long-term survival [153].

Dose intensification of daunorubicin during induction is not a new idea. Greene et al. [154] studied daunorubicin as a single dose of 180 mg/m^2 in 1972. Only a 25% complete response rate was obtained in 16 previously untreated patients aged 26–73 years. Seven of the 16 patients died during induction therapy and the rest suffered unacceptable toxicity.

Taken together, these data indicate that daunorubicin, 90 mg/m^2/daily × 3, is superior induction therapy for AML patients <60 years of age, compared with 45 mg/m^2. What is not clear is whether the higher dose is better than daunorubicin 60 mg/m^2 or a standard dose of idarubicin [155].

Daunorubicin, standard dose, and cytarabine were prospectively compared in six major randomized studies with an identical regimen except for the substitution of idarubicin, standard dose, for daunorubicin [156–162]. There were no significant differences in toxicity between the two treatments in any of the studies. In three of the studies [157–159] the complete response rate was superior with idarubicin plus cytarabine and the differences were significant for patients under the age of 60 years, and disease-free and overall survivals were significantly greater in idarubicin-treated patients in three of the studies [157, 158, 161]. The idarubicin–cytarabine regimen was significantly more effective in remission induction in patients with hyperleukocytosis than the daunorubicin–cytarabine regimen in the two studies in which that question was examined [157, 158]. In an Italian study for patients over the age of 55 years no difference in response rate or duration or survival was noted between the two treatments, but a significantly greater number of complete responders achieved remission with one course of idarubicin and cytarabine than with daunorubicin and cytarabine [161] and in a Japanese study no differences in outcome were noted [162]. In the ECOG study [156] of 349 patients over the age of 55 years the complete response rates were 40%, 43%, and 43% with the daunorubicin, idarubicin, and mitoxantrone regimens, respectively, and the differences were not significant. The median disease-free survival was 5.7, 9.7, and 6.9 months, respectively, but again the differences were not significant. A recent meta-analysis reported that idarubicin in induction therapy prolonged overall survival and disease-free survival, increased the complete response rate, and reduced the relapse rate compared with daunorubicin, although toxicity was greater with the former [163]. For patients under the age of 70 years the differences in complete response rates were greater (46%, 53%, and 52%, respectively), but the differences were still not significant. These data taken together strongly suggest that idarubicin is a more effective anthracycline than daunorubicin in the treatment of adult AML, especially in younger patients, and this fact was confirmed by a meta-analysis of 1052 patients randomized to receive daunorubicin or idarubicin, both at standard dosing, with cytarabine [164]. These clinical observations are consistent with the more favorable clinical pharmacokinetics of idarubicin [165] compared with those of daunorubicin, and with the observation that the intracellular accumulation of idarubicin is decreased to a much lesser degree by P-glycoprotein than that of daunorubicin [166].

Many investigators interpret currently available data to suggest that idarubicin should replace daunorubicin in the treatment of adults with AML, and an appropriate treatment regimen is detailed in Table 20.1.

In three randomized, prospective large studies the combination of mitoxantrone and cytarabine was compared with daunorubicin and cytarabine for induction therapy in adults with AML [156, 167, 168]. The standard dose and schedule of cytarabine were employed and mitoxantrone 12 mg/m^2 given daily for 3 days was substituted for daunorubicin in one arm of each study. No significant difference in outcome with respect to complete response rate, disease-free or overall survival, or toxicity was observed in any of the studies.

The addition of etoposide to the standard daunorubicin and cytarabine regimen improved disease-free and overall survival without improving the response rate, especially in patients less than 50 years of age in one study but not in others [169, 170].

Holowiecki et al. [171] reported that the addition of cladribine to a standard daunorubicin and cytarabine induction regimen increased the complete remission rate and overall survival at 3 years compared with the two-drug regimen in 652 newly diagnosed patients with AML ≤60 years of age. The survival advantage for the three-drug regimen was noted in patients ≥50 years of age, those with hyperleukocytosis, and those with unfavorable cytogenetics. These results deserve confirmation.

Hills et al. [172] performed a meta-analysis of studies in which gemtuzumab ozogamicin 3 mg/m^2 or 6 mg/m^2 was added to standard induction therapy or not, for adults with AML, and found that the agent prolonged survival at 5 years in patients without unfavorable cytogenetics. Both doses resulted in the same outcome but the lower dose was less toxic, as found in other studies [173]. This agent is no longer available in the USA but it clearly deserves further study.

Zeidner et al. randomized 165 newly diagnosed patients aged 18–70 years with intermediate or poor cytogenetics to cytarabine, 100 mg/m^2/day, as a continuous intravenous 7-day infusion plus daunorubicin, 90 mg/m^2, or a cyclin-dependent kinase inhibitor, alvocidib (formerly known as flavopiridol), together with cytarabine and mitoxantrone (FLAM). The complete response rate with FLAM was 70% compared with 46% for high-dose daunorubicin and cytarabine [174]. Further study of alvocidib in AML is planned.

Ravandi et al. [175] studied 62 patients with previously untreated AML with a median age of 53 years with the FLT3-ITD inhibitor sorafenib, cytarabine, and idarubicin. FLT3 mutations were present in 23 patients and 10 had unfavorable cytogenetics. A complete remission was obtained by 79% and an additional 8% attained a complete remission with incomplete platelet recovery. Interestingly, a 95% complete response rate was achieved in the patients with FLT3-ITD mutations. With a median follow-up of 52 months, the median survival for all patients was 29 months. Although this was a small study, it clearly suggests that sorafenib in

patients with FLT3-ITD mutations deserves further study. Other inhibitors of FLT3-ITD have yielded impressive results as well [176, 177].

High-dose cytarabine in induction therapy has been evaluated in a number of studies. In two early studies it was associated with greater toxicity than standard-dose cytarabine but there was no improvement in complete response rate or survival [178, 179] and a meta-analysis involving 5945 patients concluded that high-dose cytarabine led to a lower relapse rate than did standard-dose cytarabine but no improvement in complete response rate or overall survival [180]. In a more recent study, high-dose cytarabine produced a higher complete response rate and better overall survival especially in patients younger than 46 years and in patients up to 60 years of age with unfavorable cytogenetics or FLT3-ITD mutation [181]. In the most recent study [182] no advantage for high-dose cytarabine in induction was observed. High-dose cytarabine during induction is not recommended.

The addition of sorafenib, a tyrosine kinase inhibitor, to standard induction therapy led to significant improvement in event-free and overall survival after a median follow-up of 36 months, compared with placebo in one study of 267 evaluable patients ≤60 years [183]. Grade 3 or 4 toxicity was significantly higher in the sorafenib group, however.

Toxicity of Induction Therapy

Virtually all patients treated with the regimen recommended in Table 20.5 will develop total capital alopecia, which is often more disconcerting to young men than to others. Attempts to prevent alopecia with scalp tourniquets or hypothermia caps are ill advised during leukemia treatment since the scalp may become a pharmacologic sanctuary when such methods are employed.

Moderately severe nausea and vomiting accompanies induction therapy in approximately 80% of patients not premedicated with antiemetics. Older patients tend to have a lower incidence of emesis, perhaps due to poorer blood supply to the chemoreceptor trigger zone of the brain. Modern antiemetics, such as ondansetron [185] and granisetron [186], usually completely eliminate vomiting during induction therapy. It is not necessary to include dexamethasone in the antiemetic regimen, and it may indeed be unwise to do so since glucocorticoids inhibit anthracycline reductase activity, which may result in decreased anthracycline effectiveness.

Stomatitis, esophagitis, and diarrhea are usually only of grade 1–2 intensity and can be expected in approximately 65%, 15%, and 80% of patients, respectively [158]. Oral mucosal ulceration is usually well managed with viscous xylocaine or a paste of gelatin, pectin, and carboxymethyl cellulose. Hepatic toxicity manifested by serum liver enzyme elevations occurs in half of patients and is usually unaccompanied by clinically significant hepatic dysfunction and virtually always resolves with the completion of induction therapy.

A generalized mild-to-moderate erythroderma may result from cytarabine or idarubicin treatment, and a unique cutaneous eruption has been reported after etoposide administration [187].

Profound bone marrow hypoplasia and pancytopenia are expected and desirable after induction therapy since, except in patients with the M3 subtype, complete remission is virtually never achieved without these results of therapy. Pancytopenic patients will require platelet transfusion and, very likely, packed red cell transfusion until the bone marrow recovers, usually in 3–4 weeks after the end of treatment. Transfusion support is discussed in Chaps. 56 and 57.

Table 20.5 A standard remission induction regimen for adult AML

A.	Idarubicin (12 mg/m^2) is given daily on each of the first 3 days of treatment. The drug is given as an injection over 10–15 min into a central venous catheter. Severe paravenous tissue damage may result from extravasation. Consider daunorubicin 60 mg/m^2 on the same schedule as an alternative anthracycline for patients <60 years old. Consider oral hydroxyurea [184] or leukapheresis for patients with a WBC > 50,000/μL prior to initiation of induction therapy
B.	Cytosine arabinoside is given as a continuous 7-day intravenous infusion at the rate of 100 mg/m^2 per day beginning on the first day of idarubicin administration. The infusion must be controlled by an electronic device to ensure the proper rate of administration
C.	Consider adding a FLT3-ITD inhibitor for patients with that mutation and intermediate cytogenetics

Response to Induction Therapy

Approximately 90% of patients who achieve complete remission will do so within the month after completion of the first induction course. Another 10% of patients who ultimately obtain a complete remission will require a second induction course to do so. The second course should be given in the same doses and schedule as the first. Patients who fail induction therapy with two courses of idarubicin and cytarabine may be candidates for regimens employing mitoxantrone [188], carboplatin [189], 2-chlorodeoxyadenosine [136], fludarabine [137], high-dose cytarabine [138], gemtuzumab ozogamicin [190], an investigational agent, or bone marrow transplantation, all of which are discussed next. Unfortunately, patients who fail initial therapy are not likely to subsequently do well, and at the present time it is difficult to recommend a standard approach to such patients [194]. Clinical trials should always be made available to patients who fail standard induction therapy.

Often the first sign of complete remission after induction therapy is a spontaneous rise in the platelet count. If the

marrow aspirate demonstrates repopulation with normal elements at that time, and leukemic cells are rare, blood counts should be observed until they are normal. At that time another marrow aspirate should be examined to diagnose complete remission or persistent leukemia. No additional induction therapy is necessary if the former pertains, whereas the second induction course should be administered if less than complete marrow remission has been achieved. If residual leukemia without any evidence of maturation in the granulocyte series appears to be present in the first postinduction marrow aspirate, another aspirate should be examined several days later, before reinstituting induction therapy. This is necessary because a marrow recovering from anthracycline drug administration may appear hypocellular and frankly leukemic, but normalize without further therapy. Indeed, an occasional blast may even be found in the blood after anthracycline therapy in a patient who subsequently manifests complete remission without further therapy. In such patients the platelet count may begin to rise, followed within a week by a rise in the granulocyte count. Progressive improvement in both to normal levels as indicated by daily blood counts is usually a harbinger of complete remission. A transient platelet count elevation, often without a concomitant rise in granulocyte count, usually indicates an incomplete response to induction therapy. This must be confirmed by bone marrow examination when the progressive platelet count improvement levels off or reverses. Almost always the marrow examination will confirm an incomplete response in that situation. However, rarely the marrow examination may lead to confusion due to the presence of a megaloblastic maturation arrest in the granulocyte and erythroid series and no evidence of leukemia. In such cases the patient may be folate depleted, especially if significant mucous membrane toxicity occurred during treatment. Such patients may have a dramatic response to daily physiologic doses of parenteral folate, with morphologically normal marrow and normal blood counts evident 10–14 days after initiation of folate therapy. In other cases, all criteria for the diagnosis of complete remission may be present except for the continuation of significant thrombocytopenia and a continuing need for platelet transfusion despite an adequate number of megakaryocytes in the marrow. Most such patients will respond with a normal platelet count to daily, oral low-dose cyclosporin A administration (100–200 mg per day) for unknown reasons [195]. In such patients, cyclosporin A may need to be continued indefinitely. Such patients are designated CRp in many studies [107, 108] and may have impaired long-term prognosis [109]. These guidelines for reassessing the marrow after induction therapy will reduce the number of patients who receive a second induction course needlessly. The common practice of reassessing the marrow at day 14 makes no sense at all [196–198] and has led to overtreatment of many patients.

Many prognostic factors influence induction therapy results. There is an inverse relationship between time to achieve complete remission after one course of chemotherapy, and disease-free and overall survival in patients with AML [199]. The patient's age has the most consistent influence on results. Elderly patients, especially those older than 70 years, are less likely to withstand the severity of treatment [200, 201]. It is not entirely clear why this is so, but other coincidental medical problems such as cardiopulmonary disease common in the elderly may make them less likely to sustain treatment without intolerable toxicity. Poor marrow reserve usually found in the aged may delay or disallow bone marrow recovery after treatment and facilitate infectious complications. In addition, poor-prognosis karyotypes are more frequent in the elderly, whereas good-prognosis karyotypes are more frequent in young adults [200]. For these reasons and others, some have advocated less intensive therapy for elderly patients [202]. Others disagree [203]. Clearly, elderly patients require the maximum in supportive care if intensive treatment is to be given. When intensive treatment is given in a setting of maximum supportive care it is likely to be successful in elderly patients and is likely to yield more benefit than less aggressive therapy without additional significant toxicity [203–205]. In the near future, peripheral blood testing for the absence of minimal residual disease by quantitating the level of molecular mutations that remain after therapy may become the accepted method of documenting response to therapy [198].

Although in many studies remission duration in the elderly treated with standard induction regimens has been poor [200], remission duration and survival have been prolonged in others [205]. Elevated blood urea nitrogen concentration, poor performance status, high peripheral blood blast count, and hepatomegaly have been reported to be particularly poor prognostic factors for survival in the elderly with AML [206]. The treatment of elderly patients is more fully discussed below.

Patients with secondary AML, discussed in Chap. 24, and AML developing after a preleukemic phase or myelodysplastic syndrome [207] have a poorer response rate, response duration, and survival than do patients with de novo AML.

The bone marrow and blood become normal morphologically and the quantities of various cellular elements normalize absolutely and relative to each other in the majority of patients when complete remission is achieved. Some complete responders, however, manifest myelodysplastic changes permanently after stem cell damage from chemotherapy but produce normal blood cells in normal numbers [208, 209]. Remission is usually explained by the premise that chemotherapy kills most of the abnormal cells and allows residual normal stem cells to repopulate the marrow and function normally. However, some evidence suggests that remission may result from maturation and

differentiation of leukemia cells induced by standard chemotherapy [210–212]. Rarely, patients in remission are noted to have Auer rods in otherwise normal granulocytes [212, 213] and some patients have been noted to degranulate mature granulocytes before other evidence of relapse is apparent. In addition, the normal leukocytes of some patients in remission express reverse transcriptase activity characteristic of leukemic cells and uncharacteristic of normal leukocytes [214]. These observations, together with the fact that a large number of agents, including many chemotherapeutic agents, are known to cause differentiation and maturation of leukemic cells in vitro [215, 216], suggest that remission does not necessarily derive from the cytotoxicity of induction therapy alone.

Postremission Therapy

It is universally agreed that postremission therapy prolongs complete remission and enhances the cure rate in AML. From the mid-1960s until recently, myriad maintenance regimens were tested. These regimens were usually given for a finite period each month, were usually less intensive than induction regimens, and usually consisted of multiple drugs most of which were not given during the induction phase of treatment. These treatments may have had a minimal favorable effect on remission duration [217], but were largely unsuccessful. The value of such treatments became even more doubtful when it was demonstrated that the frequency of their administration had no effect on remission duration [136]. Furthermore, some studies during that period suggested that remission duration was not adversely affected by omitting maintenance therapy altogether [218, 219]. Confusion was further compounded by the fact that most studies initiated after 1979 gave better remission duration results than previous studies irrespective of postremission therapy schemes. Most of those studies have employed an intensive induction regimen with an anthracycline and cytosine arabinoside in a schedule and doses similar to the treatment in Table 20.5. Not only have those studies resulted in superior response rates and durations compared with previous ones, but also the number of disease-free long-term survivors resulting from them was significantly greater [136, 138]. These observations suggest that the efficacy of induction chemotherapy is one important determinant of remission duration. This concept is further supported by several idarubicin studies [157, 159]. Such has also proved to be the case in other highly treatable hematologic neoplasms such as advanced Hodgkin's disease. Some biochemical substantiation of that contention has been offered by Rustum and Preisler [220], who found that patients with the longest remission durations were those whose pretreatment leukemic cells best activated cytosine arabinoside to cytosine arabinoside triphosphate and retained the activated compound longest intracellularly.

It has been suggested that postremission schemes as described previously are ineffective not because the concept of postremission therapy is wrong, but because the treatments were less intensive than necessary for optimal results. Therefore, a number of studies employing postremission schemes for a finite period that were at least as intensive as induction therapy were instituted [138, 221–226]. The results of such studies have been very impressive. Median durations of complete remission on the order of 18–24 months have been obtained and 20–45% or more of complete responders so treated have remained disease free for at least 15 years [227] after achieving complete remission. The intensive postremission programs, in general, produce results superior to those obtained with previously employed lower dose postremission therapy.

Four types of successful postremission therapy have emerged from studies conducted over the last 25 years. Consolidation therapy, which is usually given as one or more courses of high-dose cytarabine with or without other agents, has become a standard form of treatment [221, 222, 224, 228]. Such programs appear to be most effective when the dose of cytarabine is 1–3 g/m^2 given every 12 h, and doses of 3 g/m^2 are commonly employed on that schedule in patients under 60 years of age [164] while doses of 1.0–1.5 g/m^2 are used for elderly patients [156]. However, the optimal dose between 400 mg/m^2 and 3 g/m^2 on such schedules remains to be determined. This is important, since cytarabine toxicity escalates steeply above doses of 500 mg/m^2 given twice daily [229]. Treatment with a high-dose consolidation program is outlined as option I in Table 20.6. Other more complicated regimens have been studied [223, 230], but results are similar or inferior to those obtained with the regimen in that table.

High-dose cytarabine-based consolidation programs that employ cytarabine doses of 3 g/m^2 are toxic and associated with a death rate during remission of approximately 10%. Patients with hepatic or renal dysfunction and older patients tolerate this treatment especially poorly. Older patients are especially prone to severe neurotoxicity from this treatment [222, 266]. Whether cytarabine 3 g/m^2 in multiple doses is more effective than lower doses, such as 1 g/m^2, as consolidation therapy is the subject of much debate [267]. Others have employed lower doses of cytarabine without apparent loss of efficacy, although the lower doses have never been prospectively compared with doses of 1 g/m^2 or higher. Neither GM-CSF [141] nor G-CSF [268] has been particularly useful during the consolidation phase of treatment.

A less toxic but effective approach to postremission therapy utilizes conventional doses of cytarabine and 6-thioguanine given on an open-ended schedule until marrow hypoplasia is achieved [138] and is summarized as option II in Table 20.6. This treatment is associated with only

Table 20.6 Postremission therapy options for adult AML patients in first remission [231]

I. High-dose consolidation therapy of short duration
Example: adapted from Mayer et al. [222]
Regimen: Cytarabine, 3 g/m^2, is given as a 3-h infusion every 12 h on days 1, 3, and 5 for a total of six doses per course, beginning within 1 month of complete remission. Courses are repeated every 28–35 days, depending on marrow recovery. A total of four courses are given
Comment: This regimen resulted in a 44% projected disease-free survival at 5 years for patients 60 years of age or less [222]. Results were significantly poorer and toxicity was prohibitive in older patients. Toxicity was significant in patients over the age of 45 years. Therefore, the regimen may only be generally applicable to patients <60 years old. Serious neurotoxicity (usually cerebellar ataxia) occurred in 12% of patients and was permanent in 40% of patients who experienced it. Other serious toxicity included confluent maculopapular rash and desquamation, conjunctivitis, pulmonary fibrosis, and gastrointestinal tract ulceration. Treatment-related death occurred in 5% of patients. Most effective in patients with favorable cytogenetics
II. Intensive recurring regimen given on an open schedule for 3 years
Example: Dutcher et al. [138]
Regimen: Cytarabine, 100 mg/m^2, as an i.v. bolus and oral 6-thioguanine, 100 mg/m^2, are both given every 12 h until severe marrow hypoplasia is achieved. The treatment is given every 3 months for 3 years beginning 1 month after complete remission is established
Comment: Approximately 10 days of treatment is required to achieve marrow hypoplasia with the first several courses, but only 5–7 days of treatment is necessary after 12–18 months. Results are equal in younger and older patients up to age 75. Toxicity is virtually limited to the bone marrow, and only 1% drug-related deaths during remission have been noted in recent years. An observed 20% disease-free survival at 15 years has been reported [227]
III. Allogeneic myeloablative stem cell transplantation
Examples: Young et al. [232], Clift et al. [233], Bortin et al. [234], Zittoun et al. [235], Cassileth et al. [236], Sakamaki et al. [237]
Regimens: The patient's marrow is ablated with high doses of chemotherapy (usually alkylating agents) with or without total-body irradiation. In some studies ablation with irradiation + alkylating agent resulted in superior relapse rate, disease-free survival, and overall survival compared with alkylating agent ablation only [238]. Marrow or peripheral blood stem cells from an HLA-identical sibling or other source are used in this procedure. Long-term results have been reported to be best in patients without ABCG2 overexpression with intermediate- or poor-risk cytogenetics and age ≤50 years [239, 240]. Long-term results are poor (67% relapse rate) in patients with molecular evidence of minimal residual disease despite morphologic remission at the time of transplant [241]. There is considerable disagreement in the literature as to which AML patients in remission should undergo this procedure [242–248]. Haploidentical donors and matched unrelated donors may give similar results [249, 250]
Comment: The probability of disease-free survival at 5 years has been estimated to be 45–60%, and treatment-related mortality in remission has been reported to be 25–40% in various studies. Results vary inversely with age, and patients over the age of 45 years do less well. For logistical and other reasons, some patients for which this therapy is planned may never receive it [251]
IV. Allogeneic reduced-intensity stem cell transplantation
Examples: McClune et al. [252], Hemmati et al. [253], Ringdén et al. [254], Pagel et al. [255]
Regimens: Less intensive chemotherapy, usually without radiation
Comment: Performed with related or unrelated donors with similar results. Less nonrelapse mortality than with myeloablative conditioning and similar disease-free survival. Three-year overall survival rates of 45% are reported [256]. This procedure is often recommended for elderly patients [257] and other poor-risk patients [240]. There are no studies comparing reduced-intensity stem cell transplantation with chemotherapy alone
V. Cord blood allogeneic stem cell transplantation
Examples: Sanz et al. [258],Verneris et al. [259], Ballen and Lazarus [260, 261]
Regimens: Cyclophosphamide plus TBI ± fludarabine, as an example
Comment: Leukemia-free survival of 40–50% at 2 years has been reported, but nonrelapse mortality has been high and as many as 1/3 of survivors have extensive chronic GVHD. Marrow recovery in the recipient may be delayed.
VI. Autologous bone marrow transplantation
Examples: Gorin et al. [262], Körbling et al. [263], Zittoun et al. [235], Cassileth et al. [236], Czerw et al [264], Mannis et al [265]
Regimens: Preparation of the patient is similar to that for allogeneic transplantation. Marrow must be harvested from the patient after complete remission is achieved and before high-dose postremission chemotherapy
Comment: Long-term disease-free survival comparable to that obtained with allogeneic marrow transplantation has been reported by various authors. Autologous transplantation is much safer than allogeneic transplantation, with only 3–5% treatment-related deaths during remission observed with the former. Autologous marrow transplantation may, therefore, be preferable for older patients. The relative merits of both major types of marrow transplantation and other high-dose cytarabine-based postremission options have been prospectively evaluated by several large cooperative group studies. Most such studies show no difference in overall survival rates. Whatever advantage in DFS is provided by stem cell transplantation is usually offset by toxic deaths

a 1% death in remission rate and can safely be given to patients up to the age of 75 years. Long-term results are excellent, but this approach has never been prospectively compared with a high-dose cytarabine-based regimen.

Allogeneic bone marrow transplantation after marrow-ablative therapy is described as option III in Table 20.6. Best results have been reported in young patients, and most reported series are heavily weighted with such patients. Preparative regimens usually consist of alkylating agents such as busulfan and cyclophosphamide or busulfan and total body irradiation. The latter was more effective than the former with respect to relapse rate, disease-free survival, and overall survival in a prospective, randomized study of patients with AML [238]. With currently available techniques, patients under the age of 60 years, who have an HLA-compatible sibling donor whose blood

lymphocytes do not react with those of the potential recipient in mixed lymphocyte culture, are considered optimal candidates for the procedure. Postremission consolidation therapy with high-dose cytarabine before allogeneic marrow transplantation for AML in first complete remission does not improve outcome compared with proceeding directly to transplantation after recovery from induction therapy [269]. Allogeneic transplants are more successful when the donor is less than 40 years old [270]. Thus, only 20% or less of patients with AML who achieve complete remission can be considered optimal candidates for allogeneic marrow transplantation using a sibling donor at this time, and some of them actually are not transplanted due to logistical and other problems [251].

Allogeneic bone marrow transplantation utilizing an HLA-matched unrelated donor has been studied in patients who do not have a sibling donor. In one study of 161 patients [271] leukemia-free survival at 5 years was 50 ± 12% for patients transplanted during first complete remission, and the relapse rate was 19% after a median posttransplant follow-up of 2.9 years. There was a direct relationship between the duration of leukemia-free survival and the dose of marrow cells infused. These results closely approach those obtained with sibling allografts and represent significant improvement in the efficacy of this procedure.

Many transplant experts think that the future of allogeneic stem cell transplantation lies with cord blood and/or reduced-intensity allogeneic transplantation [272]. Early results are encouraging, but most studies are small, and no studies in which those procedures are compared with chemotherapy alone exist to date.

Relapse after allogeneic stem cell transplantation occurs at about the same rate as in non-transplanted patients. The median time to relapse after transplantation is approximately 7 months, and less than a quarter of relapsed patients survive 1 year [273].

Autologous bone marrow transplantation, option VI in Table 20.6, has been developed more recently than allogeneic transplantation as a postremission option for AML, and in some studies [235, 236, 274], but not all [275, 276], results have been equivalent to those obtained with allogeneic transplantation. Marrow recovery seems to be more rapid after transplantation with allogeneic peripheral blood stem cells compared with marrow cells [277, 278] but there may be a higher incidence of relapse with peripheral blood stem cells [279]. Autologous bone marrow transplantation with [280, 281] and without [235, 275] ex vivo purging appears to yield similar results.

Disease-free and overall survivals for AML patients transplanted with allogeneic stem cells during first remission have been reported by innumerable investigators from around the world. The 5-year disease-free survival rate projected from actuarial analysis in most studies has ranged from 30 to 50%, and relapse rates of 15–25% have been reported. Occasionally, relapses are extramedullary [282], late [283], and possibly due to induction of leukemia in the graft [284, 285]. Most adult long-term survivors of marrow transplantation have been reasonably, if not entirely, well. In one large study, patients with no recurrence of leukemia at 2 years had an overall 82% chance of being alive in complete remission at 9 years following transplantation regardless of the type of transplant. Patients allografted, however, experienced a lower frequency of late relapse than patients autografted [286]. Females had a lower relapse rate than males, an observation also reported after chemotherapy alone [100]. In another large similar study [287] of patients who were free of AML 2 years after allogeneic transplantation, mortality remained higher than in the normal population through the ninth year post-transplantation. Recurrent leukemia was the major cause of death. Haploidentical transplants may give the same results as matched sibling donor transplants [250].

There is no doubt that both allogeneic and autologous bone marrow transplantation can cure AML. The question is the relative frequency of cure from these and other methods. In an effort to answer the question, a number of prospective studies were performed in which allogeneic or autologous bone marrow transplantation and intensive consolidation chemotherapy alone were compared [197, 221, 224, 235, 288–290, 307]. The results have been quite similar in most of these trials. Allogeneic bone marrow transplantation results in fewer leukemic relapses than consolidation chemotherapy alone, but overall survival of the two groups of patients is similar, and results with autologous transplantation are often in the middle [235] with respect to relapse rate.

The high death rate during remission after allogeneic transplantation is primarily due to acute graft-versus-host disease (GvHD). Unfortunately, treatments that reduce the incidence of acute or chronic GvHD, with the possible exception of thalidomide [291], usually lead to an increased incidence of leukemic relapse [292], since the undesired GvHD effect cannot yet be fully separated from the desired graft-versus-leukemia effect of allogeneic transplantation. Some data suggest that patients with favorable cytogenetics have longer disease-free survival after either autologous or allogeneic bone marrow transplantation than with consolidation chemotherapy alone [293, 294] and that patients with unfavorable cytogenetics fare best with allogeneic bone marrow transplantation, but these data need to be confirmed in a larger series. Chronic GVHD can be a serious problem for responders to allogeneic transplantation and its incidence has increased in recent years [295]. Recent data suggest that donor EBV+ status significantly increases the risk of chronic GVHD in the transplant recipient [296], and that low-dose interleukin-2 is highly effective in controlling steroid-refractory GVHD [297]. See Chap. 50 for information on management of the transplant patient.

Treatment of Refractory and Relapsed AML

Although significant improvement has been made in the therapy of AML and the number of potentially cured patients has increased in recent years, most patients still relapse after complete remission and ultimately die of their disease [192]. However, many relapsed patients respond to reinduction therapy with durable remissions and some of them, especially those with favorable cytogenetics such as inv(16), appear to be cured after obtaining a second complete remission. Complete responses to reinduction therapy are much more common in patients who have relapsed after an initial complete response than in patients who were refractory to initial therapy [298], and more common and more durable in patients whose first remission was longer than 1 year. Drug resistance in AML may be partially due to increased glycolysis in resistant AML cells, and this abnormality may be actionable [299].

Patients with relapsed or refractory disease are candidates for further therapy unless serious comorbidities or residual toxicity from prior therapy prevents it. Relapsed patients whose first remission was >1 year are usually retreated with the same induction regimen to which they initially responded. Others are candidates for regimens that they have not previously received followed or not by stem cell transplantation, or stem cell transplantation alone. The longer the first remission and the younger the age of the patient, the better the results with any so-called salvage therapy. Combinations of agents such as mitoxantrone and etoposide are associated with a second complete response in 25% of patients in first relapse and a median overall survival of <8 months [300–302].

A large number of studies in relapsed or refractory disease have used various doses and schedules of cytarabine with and without mitoxantrone [303]. Most yielded a complete response rate between 30% and 50%, depending on patient age and other prognostic factors. No such regimen appears to be superior to another. Although these regimens are popular in various quarters, they leave much to be desired. Relapsed or refractory patients with AML should be seriously considered for clinical trials, since to date there is no standard approach to them.

The combination of fludarabine, cytarabine, and G-CSF has been found to be quite active in poor-prognosis AML. The combination of nucleosides results in enhanced intracellular accumulation of Ara-CTP, the intracellularly active form of cytarabine, and increased DNA damage. G-CSF was thought to enhance the cytotoxicity of cytarabine by recruiting cells into the S-phase of the cell cycle and render them more sensitive to cycle-specific drugs [191, 233], but it does not appear to do this sufficiently to improve clinical results [234]. Results appear to be excellent with this regimen, with or without G-CSF, although it is quite toxic. Opportunistic infections with unusual organisms are rare but severe neurotoxicity [304–306] detracts from its appeal. Furthermore, fludarabine-based induction therapy does not overcome the negative impact of multidrug resistance proteins' overexpression [307].

The addition of gemtuzumab ozogamicin [193] to intensive reinduction therapy may improve those results and allow more patients to survive long enough to receive a stem cell transplant [308]. Recently, high-dose cytarabine, mitoxantrone, all-*trans* retinoic acid, and gemtuzumab ozogamicin was studied in 93 patients aged 18–60 years who were refractory to one cycle of standard induction therapy. The complete response rate was 51% and for patients who responded to this regimen and went on to an allogeneic stem cell transplant the 4-year survival rate was 49% [309]. These results are excellent and deserve confirmation. Others have reported similar results with a fludarabine-containing regimen [310]

Therapeutic results for patients with core-binding factor AML in first relapse are more encouraging. Such patients appear to be more sensitive to gemtuzumab ozogamicin than others, and in one study of 48 patients aged 16–76 years, patients treated with regimens including that agent had a complete second remission rate of 88% and a 5-year overall survival of 51% [311]. Unfortunately, core-binding factor AML patients account for a minority of AML patients.

New agents with major activity against relapsed or refractory AML continue to be identified and recently the specificity of new antileukemic agents has improved greatly. There is renewed interest in azacitidine, which demonstrated significant activity against de novo AML in early phase II studies [312]. Recent studies in patients who relapse after stem cell transplantation [313–316] or elderly patients are encouraging [317] as are data with a similar agent, decitabine [318, 319].

Carboplatin yields complete or partial responses in approximately 30% of relapsed or refractory AML patients [320]. No combinations including this agent have been studied in this setting, however.

Selective ablation of the leukemic clone in AML is theoretically possible with an anti-CD33—calicheamicin immunoconjugate, since CD33 is expressed by most AML cells but not by normal hematopoietic stem cells [321]. Gemtuzumab ozogamicin (GO) was such a conjugate tested clinically. A complete response was reported in 30% of 142 elderly patients with AML in first relapse with that agent [322]. However, more recent studies have been very disappointing. Martin et al. [323] reported that the addition of GO to a fludarabine, cytarabine, and idarubicin regimen failed to improve the outcome of treatment for relapsed or refractory patients. Yamaguchi et al. [324] reported that GO alone had little single-agent activity in relapsed or refractory patients, and Litzow et al. [325] reported a 12% CR rate in a phase II study of cytarabine plus GO in refractory or relapsed patients.

No patients with an initial CR of <6 months or with multiple relapses responded. Löwenberg et al. [326] reported similar results in patients ≥60 years of age in first CR. It should be mentioned that the agent has occasionally been associated with veno-occlusive disease [327]. Balaian and Ball [328] observed that CD33 upon ligation with anti-CD33 downregulates cell growth in a Syk-dependent manner, and demonstrated in vitro a correlation between GO antileukemic activity and Syk expression. Blocking Syk expression rendered AML cells unresponsive to GO, but upregulating Syk by exposing the cells to azacitidine resulted in enhanced GO activity. If these results can be confirmed it would be extremely interesting to study the sequential combination of azacitidine and GO in the clinic.

FLT3 mutations occur in approximately 30% of patients with AML and are associated with shorter disease-free and overall survival after initial or relapse therapy [329] except in patients with acute promyelocytic leukemia. These findings apply especially to younger patients [330]. Pemmaraju et al. [331] reviewed the outcome of 128 patients (22 received first salvage therapy) who received FLT3 inhibitors as part of their treatment. Median overall survival was 3.1 months and 4.2 months for those without and with FLT3 mutations, respectively, and all who had FLT3 mutations achieved CR. Mori et al. [332] demonstrated that inhibition of both FLT3-wt and mutant FLT3 is necessary for maximal antileukemic effect against cells that express both types of FLT3.

Metzelder et al. [333] treated 18 FLT3-ITD + relapsed patients with sorafenib and all had a hematological response. Lee et al. [334] reported a CR of several months' duration in an elderly relapsed male with extensive leukemia cutis. Ravandi et al. [335] reported CR in all 15 FLT3-mutated relapsed patients with a combination of idarubicin, high-dose cytarabine, and sorafenib.

Sunitinib is synergistic with cytarabine against FLT3-ITD + AML cell lines, but not cell lines with FLT-wt [336], and clinical responses have been recorded in mutated FLT3 patients [337], but the agent has not been fully studied in the clinic.

Midostaurin (PK412) is a multi-targeted kinase inhibitor with activity against mutant and wt FLT3 AML. In a study by Stone et al. [338] newly diagnosed patients under the age of 61 were induced with daunorubicin, cytarabine, and midostaurin and consolidated with high-dose cytarabine. A complete response was induced in 74% of FLT3-wt and 92% of mutant FLT3 patients, and 2-year overall survival rates were 62% for the latter and 59% for the former. These positive results led to a placebo-controlled international study (CALGB 10603) of 717 patients with FLT3 mutation. In that study at a median follow-up of 57 months the midostaurin arm reduced the risk of death by 23% [177].

Lestaurtinib (CEP-701), another FLT3 inhibitor in clinical trial, was studied in AML patients in first relapse, but results were disappointing [339]. AC220 is a second-generation FLT3 inhibitor with low nanomolar potency and exceptional kinase selectivity [340] and is currently in clinical trial [341].

FLT3 inhibitors provide us with an entirely new, more specific approach to AML treatment. However, in most studies to date, FLT3-ITD inhibition has been transient and resistance has been noted early. Resistance may be due to inadequate dosing, ligand interference, presence of residual dormant FLT3-ITD+ cells, all of these, or as-yet undiscovered mechanisms. It is too early to discard any of these agents or others not discussed, and all merit further study alone and in combination with chemotherapy and/or other agents such as mTOR inhibitors.

There are few data on post-second remission therapy that suggest that one treatment is superior to another. Robles et al. [342] demonstrated that low-dose cytarabine, 10 mg/m^2 given subcutaneously every 12 h until relapse, may have resulted in a second remission duration longer than that expected from no maintenance therapy. If these data can be confirmed, postremission cytarabine will be the first agent demonstrated to prolong second remission. A surprising finding in that study was the fact that 18% of patients in the control group also had second remissions longer than the first [343], which suggests that reinduction therapy was a more effective antileukemic therapy than initial induction and postremission therapy in that group. Therefore, it is essential to perform prospectively controlled post-second remission studies if new active therapies are to be identified, rather than simply to determine "inversion" rates from uncontrolled studies.

Farnesyl transferase inhibitors such as tipifarnib and lonafarnib have entered clinical trial in AML, but to date, results have been disappointing [344–346]. The combination of simvastatin and tipifarnib may be more active than tipifarnib alone against CD34+ AML cells [347], but clinical trials have not yet been done.

A regimen of fludarabine, cytarabine, and liposomal daunorubicin was successful in refractory and relapsed patients and produced a 44% and 56% complete response rate in them, respectively [348]. Remissions were relatively short, and a more recent study demonstrated little or no activity for liposomal daunorubicin in similar patients [224].

There is no doubt that bone marrow transplantation can cure some patients with relapsed and/or refractory AML [349–352]. However, it has been suggested by some that a bone marrow-preparative regimen without stem cell support may yield results equivalent to those reported after transplantation [353]. In a study by Forman et al. [349], 12 adults with AML who failed induction therapy were treated with an allogeneic transplant from a matched sibling and 75% achieved a complete remission. One-third of the complete responders relapsed and two-thirds (ages 20–29) remained in continuous complete remission for approximately 18–108 months. In a larger Seattle study [350] that included some

older patients, allogeneic transplantation was tested in AML patients in untreated first relapse and the 5-year disease-free survival was projected to be 23%. Only one of ten patients with AML given an allogeneic transplant in second complete remission in another study [351] survived in long-term complete remission. Ipilimumab, an immune checkpoint blockade monoclonal antibody, may restore antitumor activity through a graft-versus-tumor effect in patients who relapse after allogeneic transplantation and by this mechanism restore response in such patients. The agent is under clinical investigation [354].

Autologous bone marrow transplantation for patients in first relapse or in second complete remission was studied by Petersen et al. [352]. In all patients, marrow was harvested and cryopreserved during first complete remission. The actuarial probabilities of relapse-free survival at 2 years for patients transplanted in first relapse (21 patients) or second remission (26 patients) were 45% and 32%, respectively. The outcome in patients who were in first relapse was comparable to that of other studies in which remission was induced prior to transplantation, which suggests that there is no clinical disadvantage in proceeding directly to transplantation upon the diagnosis of relapse. Early data from the same institution suggested that the addition of IL-2 to the management of autologous transplant patients in first relapse or later stages may improve outcome [355]. However, recent data suggest no benefit for IL-2 for patients in first remission after autologous marrow transplantation [356, 357].

Some data suggest that autologous stem cell transplantation may actually be more effective than allogeneic transplantation in relapsed or refractory patients [358].

Infusion of lymphocytes from the original marrow donor is highly effective in treating chronic myelocytic leukemia patients who relapse after allogeneic marrow transplantation, but donor lymphocyte infusions are less effective in treating posttransplant relapsed patients with AML [359–361]. The major problem with this form of treatment is the frequent induction of serious GvHD, which can be fatal [362]. However, such infusions can be successful, even for relapse after unrelated donor marrow transplantation [359]. Porter et al. [363] treated 23 patients with AML who relapsed after an unrelated donor marrow transplantation and 42% obtained a complete response with an estimated 1-year disease-free survival rate of 23%. Donor lymphocyte infusions may also be able to eradicate persistent disease after allogeneic hematopoietic cell transplantation [364].

Elderly Patients

Röllig et al. [365] devised a prognostic model for elderly patients with newly diagnosed AML in which karyotype, age, NPM1 mutation status, WBC, LDH, and CD34 expression were of independent prognostic significance for overall survival. This model may be useful in other studies and may be used to stratify patients in future prospective trials. Older patients with CEBPA double mutation, NPM1 mutation, and FLT3-wild type may have significantly better survival after intensive treatment than others [366].

There is no standard treatment for relapsed or newly diagnosed elderly patients (>70 years of age) with AML. As a general rule, the same intensity of treatment used for younger patients should be considered for elderly patients because results tend to be better than with less aggressive therapy for induction. However, elderly patients do not tolerate consolidation with cytarabine 3 g/m^2 and doses half that large are commonly used. As in younger patients, for patients whose initial remission was >1 year, the same induction therapy used initially will likely yield the best results for reinduction. It should be noted that many patients with late relapse (>5 years after CR) relapse with different cytogenetics than they originally displayed [367, 368] and have a poor likelihood of long-term survival after relapse. All elderly patients should be seriously considered for a clinical trial. Some data suggest that elderly patients are less sensitive to anthracyclines than younger patients [369] and resveratrol may be helpful in overcoming this relative resistance [370].

A common approach to induction therapy of elderly patients is low-dose cytarabine (20 mg once or twice a day) by subcutaneous injection for 10 consecutive days every 4–6 weeks. Although the complete response rate with this regimen is <10%, survival is better than with no treatment other than supportive care [371]. Results with new drugs may make this approach completely obsolete. Low-dose cytarabine was studied with volasertib, a selective inhibitor of polo-like kinases, and compared with low-dose cytarabine alone in a randomized study. The combination was given to 87 patients with a median age of 75 years and the complete response rate (31%) and event-free survival rate were double that obtained with low-dose cytarabine alone. Cytogenetics did not influence response. Volasertib added to the marrow and gastrointestinal toxicity of treatment, but did not lead to more deaths.

Clofarabine, a deoxyadenosine analog, was evaluated in elderly patients with AML with good results in previously untreated patients. A complete response was obtained by Kantarjian et al. [372] in 46% of 112 patients aged 60–88 years with a median duration of response >1 year. In a study by Burnett et al. [373] of 106 elderly patients a similar response rate was observed. In both studies the drug was reasonably well tolerated. Kadia et al. [374] studied an induction regimen of clofarabine and low-dose cytarabine alternating with decitabine in 118 patients aged 60–81 years followed by consolidation and maintenance therapy with the same drugs. The complete response rate was 60% overall and 50% in those with adverse cytogenetics. Overall median survival in

the complete responders was 18.5 months. They concluded that the treatment was well tolerated and highly effective in older patients with AML. Takahashi et al. [375] compared clofarabine alone to idarubicin plus cytarabine in elderly patients and found equivalent responses and survival with the two treatments, but less toxicity with clofarabine alone. In a recent study 84 patients aged 40–75 years were treated with clofarabine and cytarabine and 67% of them went on to an allogeneic stem cell transplant that was preceded by a clofarabine-based conditioning regimen. Complete remission was achieved in 60% of patients after transplantation and the 2-year disease-free survival rate was 52%. These results are encouraging, but this was a single-arm study [376] and it is unclear whether these results are better than those that would have been obtained with other treatments. The drug needs further evaluation in combination with others.

Vosaroxin is a first-in-class quinolone derivative that acts as a topoisomerase II inhibitor and does not have the cardiac toxicity of topoisomerase II inhibitors. Its toxicity is primarily hematologic. In a phase II study of 116 previously untreated patients aged 60 years or more, several doses and schedules were studied and in the best group a 35% complete response rate was obtained, with a 1-year overall survival of 38% [377]. In another study vosaroxin was found to give results no better than low-dose cytarabine [378]. Despite other trials showing some activity for this agent [379], it seems unlikely that it will have a role in the treatment of AML.

Decitabine, alone and with other agents [381–383], is currently under evaluation for the treatment of elderly patients with AML but results are too early to fully evaluate [380, 381] or disappointing [382].

Another hypomethylating agent, azacitidine, appears to be somewhat more promising in elderly patients with AML. In one study [383] azacitidine or decitabine alone yielded essentially similar results as intensive chemotherapy in elderly patients. Another study demonstrated that hematologic improvement with azacitidine short of complete response led to improved survival [384]. In a study of 149 previously untreated patients with AML and a median age of 74, including 51 patients with de novo AML considered ineligible for intensive chemotherapy, the complete response rate with azacitidine alone was 33% and the median overall survival was 9.4 months. The 2-year overall survival was 51% in responders in this single-arm study [385]. In a study of low-dose subcutaneously administered azacitidine as maintenance therapy in elderly patients in first remission after standard induction therapy [386] the median overall survival was 20.4 months. The treatment was well tolerated and seems to have been effective. Obviously further study is needed before that impression can be confirmed.

Dombret et al. [387] performed a study of 488 elderly newly diagnosed patients randomized to receive azacitidine or several conventional treatments. Azacitidine was associated with a 3.8-month improvement in median overall survival and was well tolerated. The 1-year survival rate with azacitidine was 46.5%, compared with 34.2% for the other patients. This study provides the greatest impetus for the further study of azacitidine in elderly patients with AML. Unfortunately, to date, studies of combinations of azacitidine with intensive therapy [388] or a histone deacetylase inhibitor [389] are disappointing. On the other hand, azacitidine plus sorafenib may be effective for elderly patients with FLT3-ITD mutations [390], and in patients with FLT3-ITD and NPM1 mutation, azacitidine combined with lenalidomide may be promising postremission therapy [391]. Further studies of azacitidine in AML should take into account that low miR-29c expression by leukemic cells correlates with response to azacitidine by elderly patients [392].

In an early study of the addition of gemtuzumab ozogamicin to standard induction therapy for elderly patients the combination was found to only add toxicity without any benefit [393]. However, as a single agent gemtuzumab ozogamicin significantly improved overall survival compared with best supportive care in patients over the age of 60 years [394]. The drug remains a treatment option for elderly patients who are not candidates for more aggressive treatment if it were available.

The addition of sorafenib to standard induction therapy did not improve outcome in elderly patients, even those with FLT3-ITD mutation [395], although it does so in younger patients with that mutation [396].

A very interesting compound under investigation in elderly patients with secondary AML is CPX-351, a liposomal preparation of daunorubicin and cytarabine in a 1:5 molar ratio. In a randomized study of 309 patients aged 60–75 years comparing that agent to standard administration of daunorubicin and cytarabine in a standard schedule with standard doses, the new agent proved superior in terms of overall survival, response rate, and 60-day mortality [397]. This compound is likely to become widely used for elderly patients with AML.

At least 60% of patients with AML are 65 years of age or older. They are more likely to have an antecedent hematologic disorder, unfavorable cytogenetics, and poorer performance status at diagnosis mainly due to assorted comorbidities. Many, if not most, are judged by their physician to not be a candidate for intensive chemotherapy. Those that are treated have a significantly improved overall survival [398]. On the other hand older patients have a lower complete response rate to standard induction regimens than do younger patients and remission duration is usually shorter as well. Relapsed elderly patients rarely have useful responses to reinduction therapy although this is not always the case. Newer treatments briefly described above have not had a major impact on the results of treatment in elderly patients.

Therefore, treatment of elderly patients remains a major challenge. Hopefully, some newer agents and concepts just entering clinical trial will improve results for them. In the meantime, all elderly patients judged not eligible for standard treatment should be considered for clinical trials.

It should be noted that older patients who achieve remission after intensive or other therapy achieve significant improvements in quality of life, fatigue, and physical function as do younger patients [399].

Central Nervous System Leukemia

The diagnosis and treatment of CNS leukemia are discussed earlier in this chapter. CNS leukemia is an uncommon type of presentation or relapse in adults with AML. The incidence of CNS leukemia has decreased in AML patients since the common usage of infusional cytarabine in induction regimens due to the attainment of therapeutic levels of cytarabine in the CSF with such induction therapy. Nevertheless, about 1–2% of patients who relapse will have CNS leukemia with or without marrow evidence of relapse. These are usually young patients. Intracerebral leukemia is much less common in AML than in ALL, and virtually all adults with AML with CNS leukemia demonstrate meningeal leukemia, or cranial nerve palsy or both. Irradiation of the course of an involved cranial nerve will preserve function of that nerve if done early. Cranial nerve palsy does not respond to intrathecal chemotherapy. Patients with meningeal leukemia with cerebrospinal fluid pleocytosis usually respond to intrathecal chemotherapy, usually cytarabine, and usually do not require cranial irradiation. For reasons that are not understood, patients with AML usually have longer remissions of CNS leukemia after treatment than do patients with ALL [400].

As is the case in ALL, rapid attainment of remission of meningeal leukemia, long duration of initial marrow remission, and absence of cranial nerve palsy are favorable factors for CNS leukemia remission duration after treatment.

Mixed-Phenotype Acute Leukemia

This is an uncommon form of acute leukemia accounting for perhaps 2–3% of all pediatric and adult acute leukemias. When the leukemic blast cells display cytochemical and/or immunophenotypic features of both myeloid and lymphoid blasts the leukemia is referred to as biphenotypic and when there are two populations of cells, one clearly myeloid and the other clearly lymphoid, the leukemia is referred to as bilineal. There are few data to guide treatment for these leukemias but, in general, they are treated with ALL treatment programs and therefore will not be considered further here. For a full discussion of this "entity," see Wolach and Stone [401].

Future Directions

There is considerable interest in developing molecular tests for the diagnosis of AML [402] and for the detection of minimal residual disease in patients who have achieved complete hematologic remission [403, 404]. Determining the presence or absence of minimal residual disease will allow for informed decisions about whether or not patients require further therapy to potentially achieve cure [405].

New drugs and new techniques are under investigation for the treatment of AML and some may improve therapeutics in the future. Arsenic trioxide and all-trans retinoic acid have been found to induce apoptosis in NPM1-mutated AML cells in the laboratory [406]. Whether this induction can be demonstrated in patients remains to be seen. An old drug, pyrimethamine, was found to have significant activity against human AML in two mice xenograft models [407]. This is an oral agent that could be tested in elderly patients not fit for intensive treatment. A dendritic cell vaccine is being developed for the potential elimination of minimal residual disease and may soon come to clinical trial [408]. Vaccination with polyvalent WT1 peptides in patients with WT1+ AML in remission has been carried out at several institutions and found to be safe and possibly effective [409]. Larger clinical trials will be required to fully evaluate the effectiveness of this promising approach. Blocking MNK kinase activity in an AML xenograft model with merestinib, an orally administered multikinase inhibitor, suppresses primitive leukemic progenitors from patients with AML [410]. Preclinical studies with the agent will continue and ultimately it may come to clinical trial. Another approach under investigation involves targeting miR-126 in leukemic stem cells with antagomiR-126 nanoparticles [411]. Higher expression of miR-126, a marker for leukemic stem cells, is associated with a poor prognosis in older patients with AML and a normal karyotype treated with conventional treatment. A similar approach has been demonstrated to be feasible against FLT3-ITD+ AML [412]. Although interesting, this concept is not yet ready for clinical exploration. Another novel concept, inhibition of certain mitochondrial proteases as a leukemia therapy, is under laboratory investigation and likely to undergo clinical study in the future [413]. In an intriguing study reported in abstract only to date, Hazenberg et al. [414] reported that AML patients cured after allogeneic stem cell transplant produce tumor-specific cytotoxic antibodies that kill AML blast cells in vitro and in mouse models. Perhaps such antibodies can be used to treat other AML patients. A trial in elderly patients would be of great interest.

New prognostic markers for the disease that may serve as therapeutic targets continue to be identified. CD11b expression in a meta-analysis of 2619 patients was shown to be associated with a poorer outcome in patients with AML [415]. CTNNA1 hypermethylation, found in 25% of patients with AML, is an independent predictor for poor relapse-free survival [416].

Recent data have confirmed that smoking may influence the onset and pathogenesis of AML [417]. Hopefully these observations will be more fully explored.

Survivors of AML have an incidence of oral and pharyngeal cancer significantly higher than that of the general population for unknown reasons [418]. Is there a common viral etiology to both diseases, such as HPV?

There is a high risk of hepatitis B reactivation among patients with acute myeloid leukemia and prophylaxis with anti-HVB vaccine has been recommended [419]. It should be noted that decades ago several studies indicated that chronic viral hepatitis had a *favorable* effect on AML prognosis [420–422]. Perhaps the relationship between viral hepatitis and AML should be reexamined.

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