

Review Article

*Medical Progress***ACUTE MYELOID LEUKEMIA**

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ACUTE myeloid leukemia (AML) is characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting in hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia), with or without leukocytosis. In the United States, the annual incidence of AML is approximately 2.4 per 100,000,¹ and it increases progressively with age, to a peak of 12.6 per 100,000 adults 65 years of age or older. Until the 1970s, the diagnosis was based solely on the pathological and cytologic examination of bone marrow and blood. Five-year survival rates during this period were less than 15 percent. Over the past decade, refinements in the diagnosis of subtypes of AML and advances in therapeutic approaches have improved the outlook for patients with AML. Despite these improvements, however, the survival rate among patients who are less than 65 years of age is only 40 percent. In this article, we will review the diagnostic criteria, pathology, and treatment of AML, emphasizing new findings that promise to improve the cure rates.

CLINICAL PRESENTATION

The clinical signs and symptoms of AML are diverse and nonspecific, but they are usually directly attributable to the leukemic infiltration of the bone marrow, with resultant cytopenia. Typically, patients present with signs and symptoms of fatigue, hemorrhage, or infections and fever due to decreases in red cells, platelets, or white cells, respectively. Pallor, fatigue, and dyspnea on exertion are common. Leuke-

mic infiltration of various tissues, including the liver (hepatomegaly), spleen (splenomegaly), skin (leukemia cutis), lymph nodes (lymphadenopathy), bone (bone pain), gingiva, and central nervous system, can produce a variety of other symptoms. An isolated mass of leukemic blasts is usually referred to as a granulocytic sarcoma. Hyperleukocytosis (more than 100,000 white cells per cubic millimeter) can lead to symptoms of leukostasis, such as ocular and cerebrovascular dysfunction or bleeding. There may also be metabolic abnormalities (e.g., hyperuricemia and hypocalcemia), although these are rarely found at presentation.

DIAGNOSIS

The primary diagnosis of AML rests on the morphologic identification of leukemic myeloblasts in preparations of peripheral blood and bone marrow stained with Wright-Giemsa. These cells have round-to-irregular nuclei, distinct nucleoli, and very little cytoplasm. The cytoplasm frequently contains fine azurophilic granules and a variable number of Auer bodies, or rods (azurophilic granules within lysosomes). The presence of more than 30 percent leukemic blasts in a bone marrow aspirate is required for a definitive diagnosis of acute leukemia; before therapy is initiated, however, several critical diagnostic distinctions must be made. AML must be distinguished from acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), or AML arising in the setting of MDS, because therapeutic strategies and prognosis vary considerably for these diseases.

AML can be distinguished from ALL by demonstration of definitive commitment to the myeloid lineage through judicious use of morphologic, immunohistochemical, and immunologic methods.²⁻⁴ The distinction of AML from MDS or MDS-related AML is more difficult and requires careful clinical, morphologic, and genetic analysis. MDS is characterized by ineffective hematopoiesis, and although its diagnosis rests largely on morphologic evidence of dysplastic maturation, characteristic cytogenetic lesions, including the loss of all or part of chromosome 5 (del5q) or chromosome 7, the deletion of the long arm of chromosome 20 (del20q), and the loss of Y, are found in a substantial percentage of patients. Conversion to AML is diagnosed when the percentage of myeloblasts in the marrow exceeds 30 percent. Conventional therapy for AML is much less effective against MDS-related AML, and thus it is useful to distinguish between these two conditions at the time of the initial diagnosis.

Once a diagnosis of AML is made, the morpho-

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TABLE 1. THE FRENCH–AMERICAN–BRITISH (FAB) CLASSIFICATION OF AML AND ASSOCIATED GENETIC ABNORMALITIES.

FAB SUBTYPE	COMMON NAME (% OF CASES)	RESULTS OF STAINING			ASSOCIATED TRANSLOCATIONS AND REARRANGEMENTS (% OF CASES)	GENES INVOLVED
		MYELOPER- OXIDASE	SUDAN BLACK	NONSPECIFIC ESTERASE		
M0	Acute myeloblastic leukemia with minimal differentiation (3%)	—	—	—*	inv(3q26) and t(3;3) (1%)	<i>EVII</i>
M1	Acute myeloblastic leukemia without maturation (15–20%)	+	+	—		
M2	Acute myeloblastic leukemia with maturation (25–30%)	+	+	—	t(8;21) (40%), t(6;9) (1%)	<i>AML1-ETO</i> , <i>DEK-CAN</i>
M3	Acute promyelocytic leukemia (5–10%)	+	+	—	t(15;17) (98%), t(11;17) (1%), t(5;17) (1%)	<i>PML-RARα</i> , <i>PLZF-RARα</i> , <i>NPM RARα</i>
M4	Acute myelomonocytic leukemia (20%)	+	+	+	11q23 (20%), inv(3q26) and t(3;3) (3%), t(6;9) (1%)	<i>MLL</i> , <i>DEK-CAN</i> , <i>EVII</i>
M4Eo	Acute myelomonocytic leukemia with abnormal eosinophils (5–10%)	+	+	+	inv(16), t(16;16) (80%)	<i>CBFβ-MYH11</i>
M5	Acute monocytic leukemia (2–9%)	—	—	+	11q23 (20%), t(8;16) (2%)	<i>MLL</i> , <i>MOZ-CBP</i>
M6	Erythroleukemia (3–5%)	+	+	—		
M7	Acute megakaryocytic leukemia (3–12%)	—	—	+†	t(1;22) (5%)	Unknown

*Cells are positive for myeloid antigen (e.g., CD13 and CD33).

†Cells are positive for α -naphthylacetate and platelet glycoprotein IIb/IIIa or factor VIII-related antigen and negative for naphthylbutyrate.

logic and genetic subtype must be identified. AML is a heterogeneous disease caused by a variety of pathogenic mechanisms. At a morphologic level, this heterogeneity is manifested by variability in the degree of commitment and differentiation of the cell lineage. This variability has been used to define specific morphologic subgroups. The most commonly used method of classification is that developed by the French–American–British (FAB) group (Table 1),^{5–9} which divides AML into nine distinct subtypes that differ with respect to the particular myeloid lineage involved and the degree of leukemic-cell differentiation. This distinction is based on the morphologic appearance of the blasts (Fig. 1) and their reactivity with histochemical stains, including myeloperoxidase, Sudan black, and the nonspecific esterases α -naphthylacetate and naphthylbutyrate.

In addition, immunologic methods have been incorporated into the diagnostic criteria for some FAB subgroups^{7–10} (Table 1). Cytogenetic analysis of leukemic blasts has resulted in the identification of nonrandom clonal chromosomal aberrations in a large percentage of patients with AML.^{11–13} Some of these lesions correlate with specific FAB subtypes. Moreover, several cytogenetic lesions can be used to identify subgroups of patients with distinct clinical features and therapeutic responses. Thus, cytogenetic or direct molecular genetic methods have become

an essential part of the routine diagnostic workup of patients with AML. This combination of morphologic, immunologic, and genetically based diagnostic approaches not only makes it possible to modify therapy according to the sensitivity of biologically defined subtypes, but also provides unique markers with which to monitor a patient's response to therapy.¹⁴

MOLECULAR PATHOGENESIS

The importance of specific cytogenetic lesions as powerful determinants of the therapeutic response suggests that the mechanisms of transformation associated with these lesions is likely directly to influence the sensitivity of the leukemic blasts to therapeutic agents. The implication is that if we can understand why certain genetic lesions are associated with a favorable outcome, we may be able to apply this knowledge to improve the therapeutic approach and, ultimately, the outcome among patients with AML. The recent identification of the genetic targets of common AML-associated cytogenetic abnormalities and the elucidation of their mechanisms of action have begun to provide critical insights into this issue. This approach has been best exemplified by the highly successful therapeutic use of the differentiation-inducing agent all-*trans*-retinoic acid.^{15–22} All-*trans*-retinoic acid targets the chimeric protein en-

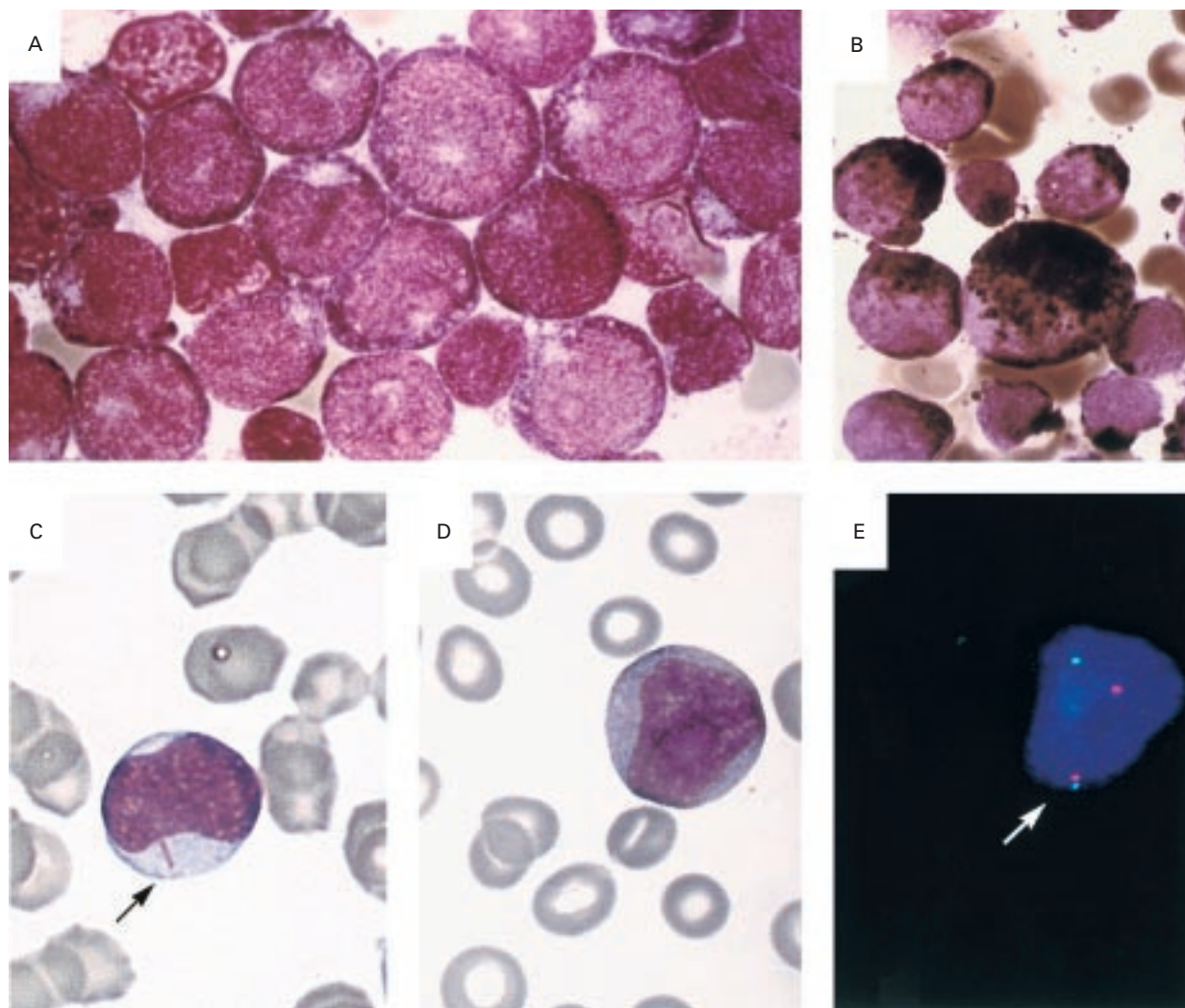


Figure 1. Cytologic Findings in Bone Marrow Specimens and Peripheral-Blood Smears from a Patient with Subtype M2 AML and the t(8;21)(q22;q22) Translocation.

In Panel A, a bone marrow specimen contains medium-sized blasts, cytoplasm with no granulation, and nucleoli that are sometimes clearly visible (May-Grünwald-Giemsa, $\times 1600$). Panel B shows a bone marrow specimen with myeloperoxidase-stained blasts ($\times 1600$). Panel C shows a leukemic blast with an Auer body (arrow) (May-Grünwald-Giemsa, $\times 1600$). Panel D shows a blast stained with May-Grünwald-Giemsa in a peripheral-blood smear ($\times 1000$). Panel E shows the results of fluorescence in situ hybridization of the cell shown in Panel D with probes specific for the breakpoint regions of chromosome 8(q22) (isolated green spot) and chromosome 21(q22) (isolated magenta spot) ($\times 1000$). The arrow indicates the chromosomal fusion (clustered green and magenta spots).

coded by the t(15;17) translocation associated with acute promyelocytic leukemia.²³

The most common targets of AML-associated chromosomal translocations are genes that encode DNA-binding transcription factors or the regulatory components of transcriptional complexes.²⁴ Transformation in each of these cases appears to result from the generation of fusion proteins that interfere in a dominant manner with the function of the wild-type protein. Study of three specific molecular ge-

netic lesions has provided critical insights into the pathogenesis of AML and has already helped to identify subgroups for therapeutic purposes.

ALTERATIONS OF AML1-CBF β

Cloning of the AML-associated t(8;21) translocation led to the identification of *AML1*, which encodes the DNA-binding subunit of AML1-CBF β , a transcription factor that regulates a number of hematopoiesis-specific genes and is essential for normal

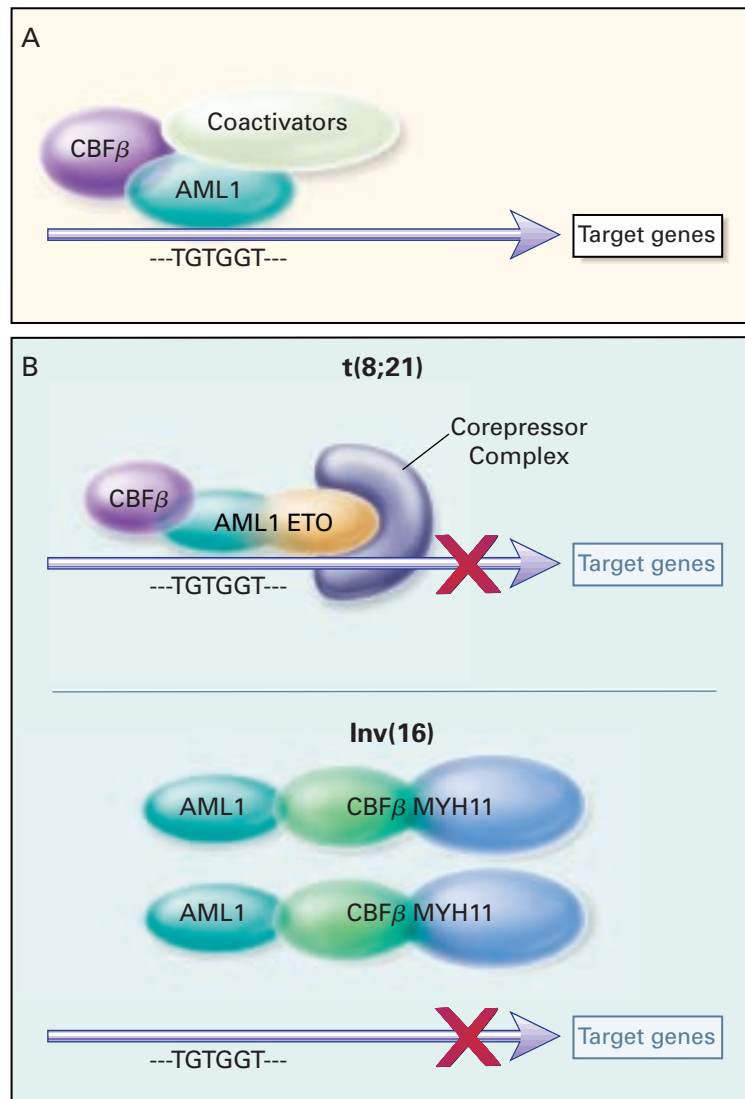


Figure 2. The AML1-CBF β Transcription Factor.

In Panel A, in normal cells, heterodimeric AML1-CBF β transcription-factor complex binds to the DNA sequence TGTGGT in the transcriptional regulatory region of AML1-regulated target genes and activates transcription through the recruitment of coactivators. In Panel B, in AML cells with the t(8;21) translocation, the N-terminal part of AML1 fuses with the C-terminal portion of ETO. The resultant chimeric protein continues to interact with CBF β and to bind to the core enhancer sequence; however, ETO recruits a nuclear corepressor complex and results in the dominant repression of AML1-regulated target genes. Similarly, the CBF β -MYH11 chimeric protein encoded by the inv(16) mutation continues to interact with AML1; however, instead of allowing AML1 to interact with DNA, this chimeric protein recruits AML1 into functionally inactive complexes in the cytoplasm.

development of the hematopoietic system.²⁵⁻³¹ Somewhat surprising was the observation that the AML-associated chromosomal rearrangement inv(16) or its variant t(16;16) targets CBF β , the other subunit of this transcription-factor complex.³² More recently, AML1-CBF β has been found to be the target of the t(12;21) translocation in pediatric ALL and a

number of rare translocations in AML, making it the most frequent target of chromosomal rearrangements in human leukemia.

The t(8;21) translocation is found in approximately 40 percent of patients with FAB subtype M2 AML, but it is not restricted to this subtype. The fusion gene created by this translocation joins the

N-terminal part of AML1, including the DNA-binding and CBF β -interaction domains, with the C-terminal portion of the 821 gene (*ETO*) on chromosome 8 (Fig. 2).^{25,26} Although the resultant protein retains the ability to bind AML1-regulated target sequences, it does not activate transcription, but instead dominantly represses AML1-mediated activation.³³⁻³⁶ Transcriptional repression appears to be mediated through the direct interaction of *ETO* with the nuclear corepressor complex.³⁷

The inv(16)(p13;q22) and the t(16;16)(p13;q22) mutations are mainly (but not only) seen in patients with FAB subtype M4Eo AML.³⁸⁻⁴¹ In these chromosomal rearrangements, the CBF β subunit of the core binding-factor complex on chromosome 16q22 is fused to the smooth-muscle myosin heavy-chain gene *MYH11* on chromosome 16p13.³² In the resulting CBF β -MYH11 chimeric product, the N-terminal portion of CBF β , including its AML1-interaction domain, is fused in-frame to a variable amount of the C-terminal domain of MYH11. CBF β -MYH11 directly represses AML1-mediated transcriptional activation, in part, by sequestering AML1 into functionally inactive complexes within the cytoplasm (Fig. 2).⁴²

AML WITH ALTERATIONS OF THE MIXED-LINEAGE LEUKEMIA GENE

Structural alterations involving band q23 of chromosome 11 are common in patients with AML and account for approximately 6 to 8 percent of primary cases and up to 85 percent of secondary cases of leukemia that develop after exposure to topoisomerase II inhibitors. This chromosomal abnormality is seen in all FAB subtypes, but predominantly in patients with M4 or M5 AML. Although more than 30 different chromosomal loci can participate in these 11q23 translocations, most sites involve 6q27, 9p22, 10p12, 17q21, or 19p13.1.^{43,44} Usually, as the result of these translocations, a chimera is formed that consists of the 5' portion of the mixed-lineage leukemia, or *MLL*, gene, fused to the 3' portion of a gene encoded on the reciprocal chromosome. The structure of *MLL* suggests that its normal function is likely to be mediated at the level of DNA or DNA-associated chromatin proteins. In addition to its activity in the regulation of gene transcription, *MLL* also directly interacts with a putative antiphosphatase called Sbf1,⁴⁵ which acts as a positive regulator in kinase signaling pathways.

Taken together, the information on the mechanisms of transformation induced by the t(15;17), t(8;21), inv(16), and *MLL* rearrangements suggests that induction of AML often results from alterations in transcriptional cascades that are normally involved in regulating decisions regarding the fate of cells. Other mechanisms that have been identified, although substantially less frequently, involve alterations of growth factor–signaling pathways including structural mu-

tations of the maturation subdomain of the receptor for granulocyte colony-stimulating factor (G-CSF).⁴⁶⁻⁴⁸

It is important to emphasize that cellular transformation is a multistep process and the abnormalities discussed above are insufficient by themselves to lead to leukemia. Thus, cooperating molecular genetic abnormalities are required. In AML, the nature of these lesions remains poorly defined. A second point to remember is that slightly more than half of all cases of AML involve chromosomal rearrangements. In the remaining cases, the underlying molecular genetic abnormalities remain to be identified.

PROGNOSTIC FACTORS

A number of clinical and biologic features that reflect the heterogeneity of AML are used to predict the likelihood that a patient will have a response to treatment.⁴⁹ Adverse prognostic factors include an age over 60 years, a poor performance score before treatment, AML resulting from prior chemotherapy or an antecedent hematologic disorder such as MDS, and a white-cell count of more than 20,000 per cubic millimeter or an elevated serum lactate dehydrogenase level at presentation (Table 2). Furthermore, an assessment for multidrug resistance and immunophenotyping may provide prognostic information. Detailed cytogenetic analysis of the leukemic blasts has also been demonstrated to provide critical prognostic information. Although there are correlations between certain FAB subtypes and cytogenetic abnormalities, such as between FAB subtype M3 AML and the t(15;17) translocation, the abnormalities themselves appear to be the more important prognostic factor.

Combining these clinical and laboratory data has allowed the subdivision of AML into three broad

TABLE 2. ADVERSE PROGNOSTIC FACTORS IN PATIENTS WITH AML.

FACTORS USED TO PREDICT RESPONSE TO INDUCTION CHEMOTHERAPY	FACTORS USED TO PREDICT RELAPSE
Unfavorable karyotype	Unfavorable karyotype
Age >60 yr	Age >60 yr
Secondary AML	Delayed response to induction chemotherapy
Poor performance score*	Features of multidrug resistance
Features of multidrug resistance	White-cell count of >20,000/mm ³
White-cell count of >20,000/mm ³	Female sex
Unfavorable immunophenotype	Elevated lactate dehydrogenase level
CD34 positivity†	Autonomous growth of leukemic cells

*The extent of a patient's disabilities are assessed according to a well-defined set of criteria.⁵⁰

†Unlike the other factors listed, this factor is considered to be minor.

prognostic groups: favorable, standard (or intermediate), and unfavorable. Although there may be subtle differences in the criteria used to define these groups, the prognostic discrimination made possible by the presence of various cytogenetic abnormalities has become more important as the efficacy of treatment for AML has improved.⁵¹⁻⁵⁴

The favorable prognostic subgroup, which includes approximately 20 percent of cases among patients who are 60 years of age or younger, is defined by the presence of leukemic blasts with the t(15;17), t(8;21), or inv(16) mutation or molecular evidence of these abnormalities. These mutations are more frequent in younger patients who have high (more than 85 percent) rates of complete remission and a relatively low risk of relapse (30 to 40 percent).

At the other end of the spectrum is the unfavorable prognostic subgroup, which includes approximately 15 percent of the cases among patients who are 15 to 60 years of age. These unfavorable cases are defined by the presence of leukemic blasts with cytogenetic abnormalities involving more than two chromosomes, monosomies of chromosome 5 or 7, deletion of the long arm of 5 (del5q), or abnormalities of the long arm of chromosome 3. These abnormalities are more frequent in older patients and in patients with secondary AML, but even among younger patients, the survival rate is less than 20 percent at five years. They represent a considerable therapeutic challenge for which no current treatment approach — including transplantation — is satisfactory.

Between these two groups are patients who are characterized as having a standard (or intermediate) risk of relapse. The leukemic blasts of these patients have either a normal karyotype or cytogenetic abnormalities that are not included in the definition of the other subgroups. In some series this includes patients with cytogenetic abnormalities of 11q23, whereas in others these patients are included in the unfavorable prognostic subgroup. Patients who are older than 60 years generally have a poor prognosis, with a probability of survival at five years of less than 10 percent.⁵⁵

SECONDARY AML

The majority of patients have no risk factors or exposures that could account for the development of the disease and thus are considered to have primary AML. Secondary AML may develop in patients with a hematologic disorder (e.g., severe congenital neutropenia) or an inherited disease (e.g., Bloom's syndrome and Fanconi's anemia), in patients who have had MDS for at least three months, or in those who have been exposed to leukemogenic agents, often as a component of therapy for an unrelated neoplasm. For example, AML can be expected to develop in 3 to 10 percent of patients who receive alkylating agents as part of their therapy for Hodgkin's disease,

non-Hodgkin's lymphoma, ovarian cancer, breast cancer, or multiple myeloma.⁵⁶ The risk of this complication peaks 5 to 10 years after the start of chemotherapy. These patients frequently present with MDS, which may then progress to overt AML.⁵⁷⁻⁵⁹ Such a course is often associated with deletions of chromosomes 5 and 7. The prognosis for these patients is considerably worse than that for patients with primary AML.

A second distinct subtype of therapy-induced AML has been identified as a complication of treatment with certain regimens of topoisomerase II inhibitors, such as the epipodophyllotoxins.⁶⁰ In contrast to alkylating-agent-induced secondary AML, this type develops after a relatively short latency period (two to three years), is not preceded by MDS, and is frequently associated with 11q23 chromosomal abnormalities.

TREATMENT

The primary objective in treating patients with AML is to induce remission and thereafter prevent relapse. Remission is conventionally defined morphologically by the presence of fewer than 5 percent blasts in bone marrow together with the recovery of peripheral-blood counts. More sensitive immunologic and molecular genetic methods are now available, which should be able to characterize remission status more accurately; however, they have not yet been extensively validated clinically. Treatment is conventionally divided into two phases: induction and postinduction.

Induction of Remission

For more than 30 years, daunorubicin and cytarabine have been the backbone of treatments to induce remission. Conventionally, daunorubicin is administered three times at a dose of 40 to 60 mg per square meter of body-surface area during each course of chemotherapy. In recent years, prospective, randomized trials of alternative agents have suggested that idarubicin⁶¹⁻⁶³ or mitoxantrone⁶⁴ is more effective than daunorubicin in younger patients, although both resulted in more prolonged cytopenia. Therefore, the question was raised as to whether the doses used in these comparisons were equivalent in terms of levels of toxicity.⁶⁵ Studies directly comparing mitoxantrone and idarubicin are ongoing.

In most induction regimens, cytarabine is given intravenously in bolus doses of 100 to 200 mg per square meter per day or by continuous infusion over a period of 7 to 10 days. Several groups have suggested that escalation of the dose during this period would be more effective than conventional dosing strategies. Two randomized trials have confirmed this notion, although the benefit consisted of extension of disease-free survival among younger patients who could tolerate the high doses used, and

it was more evident in the group with a favorable prognosis.^{53,54,66}

With the use of daunorubicin and cytarabine or their analogues, complete remission can be routinely induced in 70 to 80 percent of patients who are 60 years of age or younger and in approximately 50 percent of older patients. There is some evidence that the addition of etoposide to combinations of daunorubicin and cytarabine can further increase remission rates.⁶⁷ The use of high-dose cytarabine (3 g per square meter twice a day) did not increase the rate of remission,^{68,69} but in one randomized study it favorably influenced relapse and survival.⁶⁸

Postinduction Therapy

Once remission is induced, further intensive treatment of patients with AML is essential to prevent relapse. Three options are available for younger patients: allogeneic bone marrow transplantation from an HLA-matched related or unrelated donor, autologous bone marrow transplantation, or chemotherapy.

Allogeneic Bone Marrow Transplantation

Allogeneic bone marrow transplantation from an HLA-matched sibling has been established practice for 15 to 20 years and can cure 50 to 60 percent of recipients.⁷⁰⁻⁷² It is the most active antileukemic treatment currently available. The risk of relapse among patients in first complete remission who receive an HLA-matched transplant from a sibling is generally less than 20 percent. The reduced relapse rate is the result not only of the use of marrow-ablative high-dose cytotoxic therapy before bone marrow transplantation, but also of the allogeneic effect mediated by the graft against residual leukemia in the host (graft-versus-leukemia effect). However, this favorable effect is partially offset by the toxicity of treatment and mortality related to the complications of immunosuppression (e.g., infections with cytomegalovirus and Epstein-Barr virus) and graft-versus-host disease. Because of the possibility of graft-versus-host disease, allogeneic bone marrow transplantation is usually restricted to patients under 55 years of age.

No randomized comparison of allogeneic bone marrow transplantation with chemotherapy has been done, but patients with suitable donors have been compared with those without donors. Several studies have reported the beneficial effect of allogeneic transplantation in this type of analysis. In recent years, the use of more intensive regimens of chemotherapy has improved the results in younger patients enough so that in some studies^{66,73-75} there was no overall survival benefit for the group with donors, despite the fact that there was a lower risk of relapse.

In addition, there is increasing recognition of the prognostic profile of patients in relation to the risk of relapse.⁴⁹ Transplantation is probably unnecessary in low-risk patients in first remission, for whom the

risk of relapse is 30 to 40 percent.⁵⁴ High-risk patients do less well after transplantation than those at low or moderate risk, and the limited comparative data available do not always show a benefit after allogeneic transplantation.

Autologous Bone Marrow Transplantation

Myeloablative treatment supported by autologous stem-cell transplantation has been widely used in recent years, particularly in Europe. Several single-center series and registry data from nonrandomized studies indicate survival rates of 45 to 55 percent.⁷⁶⁻⁷⁹ Because of concern about generalized selection bias, several large collaborative trials have been undertaken. Although there were variations in study design, the main objective was prospectively to compare autologous bone marrow transplantation alone or in addition to intensive chemotherapy with intensive chemotherapy alone; patients for whom donors were available underwent allogeneic bone marrow transplantation. The French,⁸⁰ European,⁸¹ and British⁸² studies all reported a reduced risk of relapse among adults who underwent autologous bone marrow transplantation. In spite of a higher mortality rate (3 to 15 percentage points higher than the rate among patients who underwent allogeneic bone marrow transplantation), disease-free survival was also improved in two of the studies.^{81,82} Overall survival did not differ significantly, because salvage therapy with transplantation after relapse was possible in the case of some patients in the chemotherapy group.⁸¹

In a study conducted by the Pediatric Oncology Group,⁸³ the risk of relapse was reduced among children who underwent allogeneic bone marrow transplantation, but this was counterbalanced by a high risk of death (15 percent), so that the disease-free survival and overall survival were not improved. The U.S. collaborative trial⁷³ was of a similar design and found no significant difference in disease-free survival between allogeneic or autologous transplantation and intensive chemotherapy with high-dose cytarabine. Because the survival rate after relapse was better in the chemotherapy group than in the transplantation group, the overall survival was also better in the chemotherapy group. A typical feature of all these trials was that only a minority of patients who were in remission and could have undergone transplantation actually did so.

Relapse remains a problem that is partly accounted for by the presence of residual disease in the absence of a graft-versus-leukemia effect and partly by contamination of the autograft with leukemic cells. Much energy has been devoted to finding ways to purge the marrow graft of contaminating cells *ex vivo*.⁷⁹ Although gene-marking studies have demonstrated that the autograft itself can contribute to the risk of relapse,⁸⁴ there are no comparative clinical

data to confirm that techniques employed to purge the autograft *ex vivo* are effective.⁷⁹

Chemotherapy

A common feature of two of the studies in which no benefit of allogeneic bone marrow transplantation was shown was that the chemotherapy group received at least one course of high-dose cytarabine. A number of nonrandomized studies have suggested that a marked dose escalation would improve efficacy, despite the pharmacologic evidence that the intracellular concentration of the active drug metabolites reached the saturation point at doses of more than 0.5 or 1.0 g per square meter per injection.⁸⁵ The landmark study of this approach was the Cancer and Leukemia Group B (CALGB) study,⁸⁶ which demonstrated that in patients with AML in remission, four courses of cytarabine at a dose of 3 g per square meter twice daily for three out of five days was superior to equivalent courses of 400 or 100 mg per square meter given as a continuous infusion over a period of five days. The overall survival rate four years after randomization was 46 percent in the high-dose group. Another study of high-dose cytarabine⁶⁸ reported similar results, although in that study the treatment was used to induce remission.

Thus, it would appear that there is strong evidence of a dose-response effect of cytarabine in patients with AML — even in high-risk patients.⁸⁷ This approach, however, can be tolerated only by younger patients. Many questions remain to be resolved, such as the optimal dose, number of doses per course, and number of courses. There may well be different levels of benefit in the different risk groups. The results of the CALGB study suggest that those with favorable cytogenetic characteristics will benefit most. The comparative value of high-dose cytarabine regimens and autologous transplantation in the various prognostic subgroups remains the subject of study.

RELAPSE

When treatment fails in patients with AML, the available options are dictated by age, duration of the first remission, and cytogenetic findings, among other factors.⁴⁹ Patients with favorable cytogenetic characteristics — that is, a *t*(15;17), *t*(8;21), or *inv*(16) mutation — who were in remission for more than one year before relapse have an approximately 20 percent chance of survival after subsequent therapy. Since all other groups have a poor response, the highest priority should be to prevent the first relapse. For children and younger adults who have a first relapse or those who do not have a complete response to first-line induction therapy, the recommended option is marrow-ablative (high-dose) cytotoxic treatment followed by hematopoietic stem-cell transplantation, including autografts or allografts from genotypically HLA-matched related donors or phe-

notypically HLA-matched unrelated donors. Whether these patients should first receive induction therapy or immediately undergo transplantation has not been settled. Some patients may not enter a second remission and are therefore deprived of the option of bone marrow transplantation.

One study has prospectively assessed the option of offering bone marrow transplantation as immediate treatment after relapse⁸⁸ and found that survival was similar to that for transplantation after chemotherapy. However, the logistics of arranging a transplantation on short notice could be problematic. Currently, the survival rate after either autologous transplantation or allogeneic transplantation with an HLA-matched donor for patients with AML in first relapse or second remission is about 30 percent.^{89,90} Experience with the use of transplants from phenotypically HLA-matched unrelated donors or partially matched related donors is still limited.⁹¹

OLDER PATIENTS WITH AML

More than three fourths of patients with AML are older than 60 years. Only in recent years have there been studies focused on these patients. In this age group, there is an uneven distribution of unfavorable prognostic factors (e.g., cytogenetic abnormalities, features of drug resistance, or a history of MDS).^{55,92,93} In addition, older patients cannot tolerate intensive chemotherapy well and often have intercurrent medical conditions that are exacerbated by cancer chemotherapy or its sequelae. Withholding induction chemotherapy generally results in low survival rates and a poor quality of life.⁹⁴ Currently, patients older than 60 years of age who have a good performance status and meet the medical criteria of adequate organ function are usually offered induction chemotherapy and have an overall probability of complete remission of 50 percent.^{55,92,93} Among those with a complete response, approximately 20 percent survive free of leukemia for at least two years. Patients who have cytogenetic abnormalities and a high white-cell count at presentation, who are more than 80 years of age, and who are in poor general physical condition⁵⁵ or have drug-resistance phenotypes⁹² have a low likelihood of complete remission (rates of complete response are less than 30 percent).

Prognostic factors in the elderly that are associated with overall survival rates of 20 percent or more at three years include good physical condition, an age of 80 years or less, primary rather than secondary AML, the absence of cytogenetic abnormalities, and the absence of leukocytosis at diagnosis.⁵⁵ There is some evidence that the use of low-dose maintenance chemotherapy (for instance, with low-dose cytarabine) for several months after the induction of remission reduces the probability of relapse.⁵⁵ High-dose chemotherapy is highly unlikely to improve the clinical outcome in older patients.⁸⁶

Clearly, new approaches to therapy are needed to improve the cure rates in this large cohort of patients. In the meantime, the wisest course is to offer induction therapy only to patients in adequate physical condition and to proceed further only if they have a response to the first cycle of treatment without serious adverse effects.

USE OF HEMATOPOIETIC GROWTH FACTORS

The incidence of death from bacterial and fungal infections during and after induction therapy among patients with hypoplasia generally ranges from 15 percent to 25 percent among adults with AML and increases with age. Thus, the use of hematopoietic growth factors to accelerate hematopoietic recovery and prevent infection has attracted wide attention.^{95,96} G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF) can stimulate the production and activation of granulocytes and monocytes (in the case of GM-CSF) and promote their mobilization from the marrow to the blood circulation.⁹⁷ Thrombopoietin and several other cytokines have also become available for clinical studies in patients with AML. A substantial number of randomized studies have evaluated the use of G-CSF or GM-CSF as an adjunct to induction or consolidation cycles of chemotherapy.⁹⁸⁻¹⁰⁶ The duration of neutropenia was consistently shorter with the use of either cytokine. This benefit translated into fewer days of antibiotic^{99,103} or antifungal¹⁰⁶ therapy or fewer days of hospitalization¹⁰⁶ in a minority of studies. None of the studies found that this approach reduced the number of documented infections. One study reported an increase in the rate of initial response,⁹⁸ and another study reported that survival was increased.¹⁰⁰ Although AML blast cells generally express functional G-CSF and GM-CSF receptors on their surface,⁹⁷ thus far, the fear that treatment with G-CSF or GM-CSF could provoke the growth of leukemic cells in patients has not been realized.

In the light of these findings, neither G-CSF nor GM-CSF has a standard role in the clinical care of patients with AML. However, the use of these cytokines might be justified in patients with serious infections that do not respond to antimicrobial treatment. A future role for myeloid colony-stimulating factors in hematopoietic progenitor-cell mobilization is suggested by studies in which autografts of peripheral-blood progenitor cells (instead of marrow transplants) had accelerated rates of hematopoietic regeneration after mobilization with colony-stimulating factors and cytophoresis.¹⁰⁷⁻¹⁰⁹

CONCLUSIONS

In general, the trend in the treatment of patients with AML is toward the modification of therapy to treat specific subtypes of the disease and, more spe-

cifically, the targeting of the malignant cells with molecular and immunologic therapeutic strategies. The development of new drugs and treatment strategies and the circumvention of resistance mechanisms are major targets of current clinical investigation. Cross resistance of drugs to structurally unrelated cytotoxic agents — pleiotropic, or multidrug, resistance — is common in patients with refractory leukemia.^{110,111} Classic multidrug resistance (governed by the *MDR1* gene) is associated with the expression of the membrane marker P-glycoprotein. This molecule transports antileukemic drugs (e.g., anthracyclines and etoposide) out of the plasma membrane, so that high levels of expression of *MDR1* have been associated with reduced intracellular concentrations of chemotherapeutic agents in tumor cells.

Other genes involved in the mechanisms of resistance to chemotherapy and serving as predictors of treatment response are *MRP*, which codes for multidrug-resistance-associated protein, a transporter of the glutathione complex,¹¹² and *LRP*, which encodes the lung resistance protein.¹¹³⁻¹¹⁵ Although the molecular pathways leading to the development of drug resistance in patients with AML remain largely unknown, drugs that reverse or abrogate resistance are being developed.^{116,117} Phase III studies of competitive inhibitors of P-glycoprotein (e.g., cyclosporine and its analogues) have recently been initiated.

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