Acute Myelogenous Leukemia: Recent Advances in Therapy

By Richard Champlin and Robert Peter Gale

Within the last decade there has been substantial progress in the treatment of acute myelogenous leukemia (AML). In this review we critically evaluate the role of remission induction and postremission chemotherapy, immunotherapy, biologic response modifiers, and bone marrow transplantation as well as innovative experimental treatments for AML.

AML results from malignant transformation of a hematopoietic progenitor cell followed by clonal proliferation and accumulation of the transformed cells. The pathogenesis of leukemia transformation is poorly defined but is likely to be a multistep process. Fundamental to the acute leukemias is an apparent arrest in maturation early in the myeloid pathway, although some circulating granulocytes and other mature cells may be derived from the malignant clone. In 10% to 20% of patients the leukemic cells have characteristics of both myeloid and lymphoid cells. These cases have been termed hybrid leukemias or mixed-lineage leukemias. Hybrid leukemias may be biphenotypic, if a single cell displays both features, or bilineal, if different cells display myeloid and lymphoid characteristics. Bilineal leukemias can be synchronous or metachronous. Varied criteria have been used to document lymphoid and myeloid involvement. Lymphoid markers include morphology, surface antigens, terminal deoxynucleotide transferase, cytochemistry (PAS), and most recently, clonal rearrangement of Ig or T cell receptors genes. Myeloid markers include morphology (such as Auer rods and primary granules), electron microscopy, cytochemistry (Sudan black, myeloperoxidase, or nonspecific esterase), and most recently, cell surface antigens. Because of the considerable difficulty in the accurate diagnosis of hybrid leukemia we recently suggested possible criteria. Hybrid leukemias appear to be more common in AML with a monocytic component and in patients with specific cytogenetic abnormalities, including the t(4;11) and t(9;22) translocations.

Biphenotypic leukemias may represent a malignancy of pluripotential stem cells or aberrant gene expression in neoplastic myeloid or lymphoid cells.

AML is a heterogeneous disease, differing considerably among patients in respect to cytogenetic abnormalities, cellular phenotype, and response to therapy. Acute leukemias do not usually perturb normal hematopoiesis or produce symptoms until a substantial burden of leukemia cells is present, generally 10⁹ to 10¹² cells. At that point excess numbers of leukemia blasts are identified in the bone marrow, and leukemia cells enter the peripheral blood and infiltrate other tissues. The bone marrow is usually hypercellular but may be hypocellular in 5% to 10% of cases. Approximately one-quarter of patients develop AML following a myelodysplastic or preleukemic syndrome. In these patients, normal hematopoiesis is suppressed by incompletely defined mechanisms.

In most instances of AML, normal progenitor cells persist in the bone marrow that can restore hematopoiesis after effective antileukemic therapy. Rarely, patients in what appears to be complete remission have evidence of clonal hematopoiesis suggesting maturation of the malignant clone or restoration of a preleukemic state.

The goal of leukemia therapy is to eradicate the malignant cells. Treatment can be divided into several phases. The initial phase, termed remission induction, is designed to reduce the number of leukemia cells below the level of detection and restore normal hematopoiesis. By definition, no leukemia cells are detected in complete remission; however, substantial numbers of malignant cells probably persist in most patients and lead to leukemia relapse if effective postremission therapy is not administered. A variety of postremission therapies have been proposed to eradicate residual leukemia. Unfortunately, resistance to treatment commonly develops, and most patients eventually relapse despite continued chemotherapy.

Bone marrow transplantation is increasingly used to treat patients with acute leukemia. The major dose-limiting toxicity of many antileukemic drugs and radiation is bone marrow suppression. Doses of these agents can be substantially escalated if treatment is followed by bone marrow transplantation to restore hematopoiesis. Allogeneic bone...
marrow transplantation may also confer an immunologically mediated graft-v.-leukemia effect. Bone marrow transplantation has primarily been used as a form of consolidation treatment for patients in remission or to induce remission in patients with relapsed or resistant leukemia. Bone marrow transplantation may also be useful as initial therapy for selected patients with preleukemia or high-risk forms of acute leukemia unlikely to achieve remission with conventional therapy.

Although the focus of this review is on therapy for AML, it is also important to use this data to analyze critically the conduct of clinical investigations in this field. The literature describing the treatment of leukemia is complex and difficult to interpret. Many contradictory studies have been reported. Most studies reporting the highest rates for remission induction or long-term survival involve selected patients and lack randomized or concurrent controls. Many exclude high-risk subgroups such as the elderly or patients with acute leukemia after a preleukemic syndrome. In other studies such as those involving intensive postremission chemotherapy or bone marrow transplantation for patients in first remission, treatment results are distorted by selection in favor of patients in good overall condition and in remission for several months, with the exclusion of patients who relapse rapidly or have persistent infections or other medical complications. One frequent problem in the interpretation of therapeutic data in acute leukemia relates to the uncertainty in accepting the results of small, uncontrolled trials with inadequate follow-up. Preliminary results of studies suggesting a therapeutic advance are more likely to be prominently published than negative findings that may not be reported. Results published from single-institution studies generally exceed those reported by large cooperative groups utilizing similar therapies. Thus, caution is needed in the interpretation of uncontrolled studies, and results must be considered in relation to patient selection and prognostic factors.

Results of identical treatment protocols may vary substantially between centers or over time. For example, the Cancer and Leukemia Group B utilized the same remission induction chemotherapy in two consecutive trials; the remission rates differed substantially although the therapy was identical. Recently, patients entered into a large Medical Research Council trial in its second half had a significantly higher remission rate than individuals entered into the first half of the study, again despite identical treatment. These results could not be accounted for on the basis of known prognostic factors and emphasize that variables other than chemotherapy can influence the outcome of drug trials in AML. This observation suggests strongly that therapeutic trials should be prospective and randomized; trials not fulfilling these criteria must be viewed cautiously. In this review we focus, when possible, on the results of prospective controlled trials.

REMISSION INDUCTION CHEMOTHERAPY

The cornerstone of remission induction chemotherapy is the combination of cytarabine and an anthracycline. Few randomized studies comparing drug doses or different anthracyclines have been reported. The best results utilized cytarabine, 100 to 200 mg/m²/d, by constant or intermittent intravenous infusion for seven days in combination with daunorubicin, 30 to 70 mg/m²/d, by intravenous bolus on the first or last three days. Addition of 6-thioguanine or other agents has not proved beneficial. Patients who fail to achieve complete remission with one or two courses of this induction chemotherapy have a poor prognosis; even if remission is ultimately achieved, it is typically brief. This conclusion may not apply for less intensive regimens; five-day treatment schedules have also been effective in some studies but generally require multiple courses of treatment to achieve remission. Approximately half of patients who fail to achieve remission have resistant residual leukemia, and the remaining half of patients with treatment failures die of infections, bleeding, or rarely, direct toxicity of the chemotherapy.

A recent trial comparing 100 v 200 mg/m² of cytarabine given by continuous intravenous infusion showed no difference in remission rates. Daunorubicin is preferable to doxorubicin in induction chemotherapy, since its use is associated with less mucosal and gastrointestinal toxicity. The optimal dose of daunorubicin is uncertain. The drug is generally well tolerated in doses up to 60 to 75 mg/m²/d for three days in young patients, but the dose should probably be reduced in patients over 60 to 70 years of age. Except for patients with preexisting cardiac dysfunction, cardiotoxicity is unusual with cumulative daunorubicin doses <1 g/m². Cytosine arabinoside with either amsacrine or mitoxantrone appears as effective as with daunorubicin. Mitoxantrone appears to produce less mucositis than anthracyclines and is better tolerated by older patients. Several investigational anthracyclines, including idarubicin, aclacinomycin, and epidoxorubicin are currently under investigation. Some may have advantages with regard to cardiac toxicity, but most data suggest cross-resistance with daunorubicin. In one recent randomized trial, the combination of cytarabine and idarubicin produced a higher remission rate than cytarabine and daunorubicin.

Some investigators have evaluated more intensive regimens such as extending cytarabine administration to ten days. Although selected patients may benefit, this approach results in increased toxicity and a greater rate of early death without a clear improvement in the remission rate or duration. As a consequence, its routine use cannot be recommended.

High-dose cytarabine alone, with l-asparaginase, an anthracycline, amsacrine, or mitoxantrone has recently been evaluated as remission induction therapy for patients with AML. It is not certain whether these additional drugs increase efficacy. In one recent study, the remission rate with high-dose cytarabine alone exceeded 90%. Results are variable; although some uncontrolled studies report relatively high remission rates, there is no convincing evidence that survival is improved compared with that achieved with standard-dose cytarabine with daunorubicin. In addition, because of the cumulative toxicity of high-dose cytarabine, its inclusion for induction chemotherapy may limit its use during postremission treatment.

Several patient groups pose particular problems in remis-
sion induction treatment. Patients greater than 60 years of age generally have lower remission rates. This appears to be primarily due to a greater risk of early death from infection or toxicity, but disease-related factors may also be important. Elderly patients have a higher incidence of preleukemic syndromes and are more likely to have cytogenetic abnormalities associated with a poor prognosis. In two randomized studies, elderly patients receiving attenuated doses of cytarabine and daunorubicin had better results than with full-dose regimens.

Patients in whom AML develops after a preleukemic or myeloproliferative syndrome or after exposure to cytotoxic chemotherapy and/or radiation given for other malignancies (therapy-linked AML) have only a 20% to 40% likelihood of achieving remission with standard induction chemotherapy. Other patients, usually elderly, present with slowly progressive or “smoldering” acute leukemia; they also have a lower remission rate with intensive therapy. Low-dose cytarabine, 10 to 20 mg/m²/d, has been used to treat elderly patients and patients with poor-risk categories of acute leukemia; durable remissions are unusual, and most patients require at least 3 weeks of treatment, which typically results in bone marrow aplasia. There are no convincing data that low-dose cytarabine is as effective as conventional-dose induction chemotherapy for these high-risk patients, and its use is not recommended if the objective of therapy is to achieve a remission. High-dose cytarabine has also been evaluated in patients with therapy-linked AML or other poor prognostic subgroups. Although preliminary encouraging results were reported, there is no clear evidence that this approach is superior to other induction regimens.

The management of patients who develop acute leukemia during pregnancy poses special problems. The potential teratogenicity of chemotherapy is of concern during the first trimester; the incidence of fetal malformations does not appear to be increased with chemotherapy given after this time. Bleeding is an additional problem, particularly during labor, since chemotherapy produces thrombocytopenia in the fetus as well as the mother. It is often appropriate to delay chemotherapy treatment in patients presenting in the third trimester until after delivery. Leukopheresis may be useful as a temporary measure.

POSTREMISSION CHEMOTHERAPY

Further cytoreduction is probably required in patients who achieve remission to eradicate residual leukemia cells and prevent relapse. Several terms have been utilized to describe forms of postremission chemotherapy. Unfortunately, these terms are poorly defined, and their use has not been uniform. Consolidation or early intensification refers to one or more courses of therapy administered soon after achieving remission that produces severe myelosuppression. Late intensification involves one or more courses of similarly intensive chemotherapy but given after a delay of 6 to 12 months. Maintenance chemotherapy is generally conceived of as frequent courses resulting in less severe myelosuppression given over several months or years. The efficacy of these therapies in prolonging remission duration and in preventing relapse is controversial.

The median duration of remission and proportion of long-term survivors after modern remission induction chemotherapy alone is largely unknown, since almost all contemporary studies have utilized some form of postremission therapy. In one study patients induced into remission with cytarabine and daunorubicin received no further therapy. The median remission duration in 19 patients was 8 months; 12% remain disease free beyond 5 years. In a subsequent trial, a single postremission cycle reportedly increased the median remission duration to 30 months; this study was not randomized, and it is difficult to draw meaningful conclusions. Preliminary results were recently reported from an Eastern Cooperative Oncology Group study that randomized patients entering remission to no further therapy, standard maintenance, or high-dose intensive consolidation. The no-therapy arm was terminated because of rapid leukemia relapses and a median remission duration of only 4 months; this was significantly inferior to the maintenance therapy group. The consolidation chemotherapy group was not analyzed. These studies demonstrate that some form of postremission therapy is indicated to prolong remission duration.

Studies reporting the longest remission durations have utilized two or more courses of consolidation/intensification chemotherapy; the median remission duration has generally ranged from 1 to 2 years with 5-year disease-free survival rates of 10% to 25% in adults and up to 45% in children. Most studies involve two to four courses of intensive consolidation therapy using similar agents for induction. Several recent studies using high-dose cytarabine alone or with an anthracycline as consolidation have produced encouraging results with approximately 40% 3- to 5-year leukemia-free survival rates. These preliminary results require confirmation. Several randomized controlled studies of consolidation chemotherapy have been reported. These studies show a trend toward improved disease-free survival, but this has not been statistically significant in most instances.

Maintenance chemotherapy in AML has generally utilized repeated short courses of intravenous or subcutaneous cytarabine with thioguanine or daunorubicin given monthly for 2 to 3 years. Numerous controlled and uncontrolled trials with few exceptions have failed to demonstrate a substantial benefit in patients receiving maintenance therapy compared with those receiving induction and consolidation alone. A recent multicenter German study reported superior results with maintenance therapy, but this was probably due to unexpectedly poor results among controls. These data are similar to results for treatment of most other human cancers where maintenance chemotherapy generally does not prolong survival. Maintenance chemotherapy should not be routinely utilized in the treatment of AML in patients receiving intensive induction and consolidation chemotherapy.

Late intensification chemotherapy has also been reported to improve the remission duration in uncontrolled studies. Children receiving protracted regimens involving repeated cycles of intensive chemotherapy have had favorable results in some but not all studies. Adults generally
do not tolerate these regimens as well and have not appeared to benefit beyond results achieved with initial consolidation alone. Results of recent randomized trials did, however, indicate superior remission duration in adults receiving late intensification chemotherapy 1 year after achieving complete remission, although this did not reach statistical significance.32 There is considerable controversy regarding the total length of treatment and the value of late intensification for patients with acute myelogenous leukemia.

DIFFERENTIATING AGENTS

An innovative potential approach to the treatment of leukemia is to induce maturation of leukemic blasts to terminal, nonproliferative cells.105 Several agents can induce leukemia cells to differentiate in vitro, including phorbol esters, dimethylsulfoxide, and retinoids.106 Retinoic acid has been studied clinically in patients with smouldering leukemia or preleukemia, but with rare exceptions, it has not been beneficial in these settings or in typical AML.107,108 Low doses of many chemotherapy drugs are weak inducers of cellular differentiation. Low-dose cytarabine has been proposed to act by this mechanism,71 but in most patients, it appears to act through cytotoxicity to produce a hypocellular bone marrow after 2 to 3 weeks of treatment.72,73

IMMUNOTHERAPY AND BIOLOGIC RESPONSE MODIFIERS

There have been extensive attempts to utilize immunologic agents to treat AML. Initial studies utilized adjuvants and nonspecific agents such as bacillus Calmette-Guerin.109,110 Corynebacterium parvum,38 or other agents alone or in combination with irradiated or chemically modified autologous or allogeneic leukemia cells in an attempt to enhance antileukemic immunity. This form of immunotherapy alone or with maintenance chemotherapy has generally failed to prolong the remission duration.111,112

Human leukocyte interferon and recombinant α-interferon have also been evaluated but have not shown activity.113 Intravenous monoclonal antibodies reactive with AML cells have also been studied; transient reduction in circulating blasts may occur, but there is little effect on the bone marrow, and complete remissions have not been reported.114 Preliminary trials with tumor necrosis factor and with combinations of interferons are in progress.

TREATMENT OF THE CENTRAL NERVOUS SYSTEM

CNS involvement in AML is generally due to infiltration of leukemia cells into the meninges. CNS leukemia is uncommon at diagnosis. Ultimately, 5% to 10% of patients will have meningeal involvement, usually in the setting of bone marrow relapse.32,115-117 Because of this, prophylactic therapy to the CNS is generally not indicated. CNS relapse occurs most frequently in patients with myelomonocytic or monocytic subtypes; some centers recommend prophylactic local treatment in children with these subtypes.117 Treatment of documented CNS relapse usually uses intrathecal cytarabine and/or methotrexate alone or combined with cranial radiation. Although this approach can provide local control, leukemia is likely to recur; more typically, systemic relapses intervene.

PROGNOSTIC FACTORS IN AML

Numerous studies have attempted to define clinical factors predictive of either remission induction or duration.57,118-121 Potential factors involve patient- and disease-related variables. The primary patient-related factor is age.39,31,32,62-94 Elderly patients generally have lower remission rates, but in those achieving remission, its duration is not substantially different than that in young adults.39,44,119 Disease-related factors include histologic subtype.121,122 presence of a preleukemic syndrome.56,67 and evidence of extramedullary disease. Cytogenetic abnormalities may be fundamental to the pathogenesis of acute leukemia and also provide independent prognostic information.9,12 Characteristic chromosome abnormalities correlate with histologic subtypes as summarized in Table 1. Patients with t(8;21), t(15;17) and inversions or translocations of chromosome 16 have a relatively good prognosis, whereas those with -5/5q-, -7/7q-, t(4;11), t(6;9), t(9;22) tend to have a poor outcome.

The French-American-British (FAB) histologic subtype classification is of limited prognostic significance.21,122 The promyelocytic (M3) subtype is associated with a coagulopathy due to disseminated intravascular coagulation and often excessive fibrinolysis that may lead to bleeding complications during induction chemotherapy.123-127 Prophylactic heparin is widely used to suppress intravascular coagulation; although no prospective randomized trials have been performed, uncontrolled trials suggest that heparin reduces bleeding complications.123,124,126 Release of proteases from leukemic promyelocytes may inactivate fibrinolytic inhibitors such as α-2-plasmin inhibitor and lead to excessive fibrinolysis. Treatment with the combination of α-aminocaproic acid and heparin may be effective to prevent bleeding in patients with acute promyelocytic leukemia and reduce the levels of α-2-plasmin inhibitor.127 Patients with promyelocytic leukemia who achieve remission may have a longer remission duration and a longer survival time than patients in other subgroups, but this is controversial.123,124 Patients with Auer rods (M2 or M3 subtype) tend to have a better prognosis than those with myelomonocytic, monocytic, or erythroid subtypes.67,99,121,122 Acute megakaryocytic leukemia, recently defined as the

<table>
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<tr>
<th>Chromosome Abnormality</th>
<th>Histologic Subtype</th>
<th>Relative Prognosis</th>
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<tbody>
<tr>
<td>t(8;21)</td>
<td>M2</td>
<td>Good</td>
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<tr>
<td>t(15;17)</td>
<td>M3</td>
<td>Good*</td>
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<td>t(9;11) or 11q-</td>
<td>M4, M6</td>
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<td>inv or del (16)</td>
<td>M4, M6</td>
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<td>t(6;9)</td>
<td>M4, M6</td>
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<tr>
<td>+ 8</td>
<td>M1, M2, M4, M5, M6</td>
<td>Poor</td>
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<tr>
<td>−5,5q−, −7,7q−</td>
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<td>t(9;22)-Ph1</td>
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<td>Poor</td>
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<tr>
<td>Aneuploid or pleomorphic</td>
<td>M1, M2, M3, M4, M6</td>
<td>Poor</td>
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*Associated with disseminated intravascular coagulation during remission induction; may have longer duration of remission.
FAB M₇ variant,¹²⁸ may have a relatively poor prognosis.¹²⁹ Parameters related to the mass of leukemia cells such as WBC and lactic dehydrogenase, the mitotic or labeling index, abnormalities in myeloid colony formation, and response to chemotherapy in clonogenic assays in vitro have been predictive in some but not all reports and are of limited clinical utility.¹³⁰¹³⁴

The clinical significance of the hybrid leukemias with both myeloid and lymphoid characteristics is unknown.⁴ Present data suggest that these individuals, particularly those with the t(4;11) or t(9;22) translocation, are less responsive to chemotherapy and have a lower probability of long-term disease-free survival. Prospective trials have been predictive in some but not all reports and are of limited clinical utility.¹³⁵¹³⁶ Present data suggest that these individuals, particularly those with intensive chemotherapy, and CNS prophylaxis is sometimes given. It has also been recommended that trials comparing chemotherapy or transplantation in this setting have not been reported.

Several investigators have used combinations of these factors to formulate a prognostic index with the goal of identifying good- and poor-risk prognostic groups and to define patients who should receive experimental therapies or bone marrow transplantation.¹³⁷ Although these indexes can distinguish some prognostic groups, it is currently impossible to reliably identify patients who have more than a 50% chance of prolonged survival with chemotherapy. These indexes should probably not be used to assign treatment except in the context of controlled trials.

TREATMENT OF RELAPSED AML

Despite optimal initial therapy, a substantial proportion of patients ultimately relapse. The chance of achieving a second remission depends on the nature of prior treatment, the length of the first remission, and the initial response to therapy. Twenty-five percent to 50% of patients will achieve a second remission after treatment with cytarabine and daunorubicin, amsacrine, or mitoxantrone.³²⁴⁴ Extensively treated patients are less likely to respond. The median duration of second remissions is usually less than 6 months, and there is no evidence that additional chemotherapy is effective in prolonging the duration of remission.

High-dose cytarabine alone³⁵³-³⁷ or in combination with L-asparaginase,⁵⁸ an anthracycline,¹³ eightcassere,¹³⁹ or mitoxantrone⁴⁰ may increase the remission reinduction rate to 50% to 70%. The optimal dose and schedule of high-dose cytarabine are uncertain.¹⁴¹ Doses of 3 g/m² over one to three hours every 12 hours for four to six days have been commonly utilized, but comparable results have been reported in some studies using lower doses.¹²¹⁴ Higher doses result in greater toxicity. The risk of irreversible cerebellar dysfunction increases with the dose and duration of therapy.¹⁴³

Other single agents have limited activity in recurrent AML. Amsacrine,¹²¹⁴ 5-azacytidine,¹⁴³ mitoxantrone,⁵¹¹⁴⁶ homoharringtonine,⁴⁷ diaziquone,⁴⁸ cyclophosphamide,⁴⁹ etoposide,⁵⁰⁰ experimental anthracycline analogues,⁵⁴⁵⁶ or combinations of those agents¹⁵¹-¹⁵³ produce transient remissions in less than 30% of patients. Two promising regimens appear to be mitoxantrone with cytarabine¹⁴⁶ or with etoposide.¹⁵⁴

BONE MARROW TRANSPLANTATION

High-dose chemotherapy and radiation combined with bone marrow transplantation from an HLA-identical sibling is an effective treatment for AML and is the preferred therapy in selected patients.²¹-²⁴ Results are primarily related to the disease status at the time of transplantation; these data are reviewed in Table 2. Initial transplant studies involved patients with advanced resistant disease who failed to respond to standard and investigational chemotherapy. Ten percent to 20% long-term disease-free survival rates were achieved even in this unfavorable setting. Major causes of treatment failure were leukemia relapse and transplantation-related complications such as toxicity, graft-versus-host disease, interstitial pneumonitis, and opportunistic infections. Improved results have been reported in patients who received transplants earlier in the course of their disease. Approximately 30% achieve prolonged survival if transplants are performed at the time of initial relapse or in a second remission; there appears to be no advantage in administering further chemotherapy or attempting to achieve a second remission before bone marrow transplantation.¹⁴⁶

The best results of bone marrow transplantation in AML have been achieved in patients who received transplants while in first remission;¹⁵⁵-¹⁵⁸ actuarial relapse rates vary from 0% to 40%, and 40% to 70% of patients achieve prolonged, disease-free survival. Outcome is related to patient age in most studies,¹⁵⁸-¹⁶¹ with 50% to 70% survival rates in patients under the age of 30 and 30% to 45% survival rates for patients 30 to 50 years of age. Patients over 50 years of age are not routinely considered for bone marrow transplantation.¹⁶¹

Most centers utilize a pretransplant preparative regimen of high-dose cyclophosphamide and total body radiation. Some centers have evaluated alternative preparative treatments with the goal of reducing the risk of relapse. The regimen of busulfan and cyclophosphamide²¹⁄₆₂ or combining high-dose cytarabine²¹⁄₆₃ or etoposide²¹⁄₆₄ with total body radiation may provide more effective antileukemic therapy, but the overall survival is similar to other regimens. Controlled trials comparing these regimens have not been reported.

It is important to understand the mechanism of relapse after bone marrow transplantation. The vast majority of patients who relapse have recurrence in recipient cells, which indicates an inadequate antileukemic effect. In rare patients, particularly those relapsing several years posttransplant, leukemia recurrence has been reported in donor cells.¹⁶⁵

| Table 2. Comparison of Disease-Free Survival Reported for Bone Marrow Transplantation and Chemotherapy in AML |
|------------------------------|-----------------|-----------------|
| Refractory relapse           | BMT             | Chemotherapy    |
| Initial relapse              | 20-30           | <5              |
| Second remission             | 20-50           | <5              |
| First remission              | Age <30 yr      | 50-70           | 20-50             |
| Age 30-50 yr                 | 30-45           | 10-45           |

Values approximate actuarial survival ±3 years. Abbreviation: BMT, bone marrow transplantation.
These data suggest reinuduction of leukemia; alternative explanations are also possible, including transfection of oncogenic DNA or, in the case of sex-mismatched transplants, exchange of X and Y chromosomes between a residual host leukemia cell and a donor cell.

There is considerable controversy whether patients with AML in first remission who have an HLA-identical sibling should receive a bone marrow transplant at that time or whether the transplant should be delayed until relapse or a second remission. In patients <30 years of age, results of bone marrow transplantation are equivalent or superior to those achieved with chemotherapy, and its use is reasonable. Representative results for adults are illustrated in Fig 1. Three controlled studies have been reported in adults in first remission who have an HLA-identical sibling; in each study there was a significantly lower rate of leukemia relapse with bone marrow transplantation. The overall survival was higher with transplantation in each study, but the difference was significant in only one because of a higher rate of treatment-related complications with bone marrow transplantation such as graft-v-host disease and interstitial pneumonia. When one also considers that 20% to 30% of patients who relapse after postremission chemotherapy can be salvaged by bone marrow transplantation, it remains uncertain whether early bone marrow transplantation is warranted in adults in first remission (Fig 2). This question requires examination in a prospective controlled study. Based upon current data, the routine use of bone marrow transplantation cannot be recommended for patients in first remission who are older than 30. Some investigators have suggested the use of prognostic factors to identify individuals most likely to benefit from transplant chemotherapy. For example, patients with the monocytic subtype or with a high initial leukocyte count have poor results with chemotherapy. Unfortunately, these biologic factors also predict an unfavorable outcome with bone marrow transplantation.

Advances in bone marrow transplantation may alter these conclusions in the future. The use of cytomegalovirus-seronegative blood donors and prophylactic intravenous immunoglobulin may reduce the incidence of interstitial pneumonitis. Removal of T lymphocytes from the donor bone marrow can prevent graft-v-host disease; unfortunately the rate of graft rejection and the risk of leukemia relapse are increased. These problems may potentially be overcome by more effective preparative regimens, but it remains to be determined whether T cell depletion will improve survival.

Other methods to reduce graft-v-host disease are also promising; posttransplant immunosuppressive treatment with the combination of cyclosporine and methotrexate is more effective than either drug alone, and extended disease-free survival has been reported in up to 70% of patients treated with this regimen. Most patients do not have an HLA-identical sibling. As a consequence there has been considerable interest in the use of alternative donors or sources of hematopoietic stem cells for transplantation. Bone marrow transplants from related, partially HLA-matched donors have been reported. Both the risk of graft rejection and graft-v-host disease increase progressively with greater genetic disparity between the donor and recipient. Preliminary data suggest that the survival of patients receiving transplants from related donors phenotypically HLA identical or mismatched for only one HLA-A, -B, or -D locus antigen is similar to that with HLA genotypically identical grafts. Results in recipients of two or three locus HLA-mismatched transplants are poorer, particularly in adults. Some centers have attempted T cell-depleted transplants from HLA-haploidentical donors with the goal of preventing graft-v-host disease. Preliminary data indicate a high rate of graft rejection and graft-v-host disease with few survivors.

Bone marrow transplants from unrelated, HLA-identical donors have also been attempted. The considerable polymorphism of HLA loci makes this approach difficult. Preliminary data indicate that successful transplants are possible, that the risks of graft rejection and graft-v-host disease are considerable, and that survival is <20%. A very large registry of potential donors is required to identify completely HLA-matched donors. Registries of this type exist in North America and Europe. The North American registries are currently being organized into a centralized network. We recently projected the potential impact of this approach in AML if this strategy were successful.

AUTOLOGOUS BONE MARROW TRANSPLANTATION

Autologous bone marrow transplantation using bone marrow cells or, more rarely, peripheral blood cells collected and
cryopreserved while the patient is in remission has also been considered in patients with AML. At a later time, the patient receives high-dose chemotherapy with or without total body irradiation followed by reinfusion of the stored bone marrow cells. The major limitation of this approach is that the "remission" bone marrow is likely to be contaminated by occult leukemia cells. In addition, any graft-versus-leukemia associated with allogeneic bone marrow transplantation would probably not occur with autologous transplantation. There has been a high rate of leukemia relapse after autologous bone marrow transplantation in patients with advanced AML. Several approaches have been proposed to eradicate residual leukemia cells from autologous bone marrow, including treatment with monoclonal antibodies reactive with leukemia cells or pharmacological agents. Unfortunately, most antibodies reactive with myeloid leukemia cells also cross-react with normal hematopoietic progenitors. The considerable heterogeneity of leukemia cells makes it uncertain whether one antibody will react with all clonogenic leukemia cells. Recent data suggest that the phenotype of leukemia stem cells may differ considerably from their progeny. Nonetheless, a pilot study reported hematologic recovery and remissions of up to 21+ months in AML patients who received transplants in relapse or in second remission with autologous bone marrow treated with anti-AML monoclonal antibodies. Two pharmacological agents related to cyclophosphamide, 4-hydroperoxycyclophosphamide (4HC) and mafosfamide (ASTA-Z), have been used to eliminate leukemia cells from autologous bone marrow. In one recent report of 11 of 25 (42%) patients receiving autologous transplants of 4-HC–treated bone marrow while in second or third remission survived more than 1 year free of relapse; these encouraging results would not be expected with alternative therapies. A number of patients with AML have recently received autologous bone marrow transplants using untreated or mafosfamide-treated bone marrow while in first remission; unfortunately these studies were uncontrolled and involved highly selected patients so that critical evaluation of the results is not possible. An innovative method to remove leukemia cells from autologous bone marrow involves maintaining the bone marrow in long-term culture; this may allow a growth advantage for normal cells. Further studies are required to determine whether this approach is effective.

Autologous bone marrow transplantation remains an experimental approach. Further carefully conducted controlled trials are necessary to assess the efficacy of this technique and its relative role compared with alternative therapies. It is possible to envision this approach as a form of intensive postremission therapy in which one elects to give extremely high dose treatment to the vast majority, but not all, of the bone marrow with less intensive therapy to the entire bone marrow with conventional chemotherapy.

**SUMMARY**

Results of treatment of AML have improved over the last decade. With modern remission induction chemotherapy, most patients achieve complete remission. The median remission duration is now 1 to 2 years, and a substantial fraction of patients achieve long-term disease-free survival. Bone marrow transplantation provides an improved antileukemic effect compared with chemotherapy alone, and it is the treatment of choice for selected groups of patients. The major limitation is the risk of transplant-related mortality. Most patients are not currently eligible for bone marrow transplants because of advanced age or lack of a histocompatible donor. Autologous marrow transplantation may be effective in selected settings, but this remains investigational at present. Substantial improvement in results of treatment of AML requires the development of new and effective chemotherapeutic agents that are non–cross-resistant with available drugs. Results of bone marrow transplantation may substantially improve if innovative measures to prevent major complications are successful.

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R Champlin and RP Gale