The treatment of patients with acute myelogenous leukemia (AML) ranges from palliative care only, to standard therapy, to investigational approaches. Acute myelogenous leukemia is, in fact, several different diseases, and the percentage of clinical responses varies with disease and prognostic subsets.

There are three broad treatment options for patients with acute myelogenous leukemia (AML): palliative care only, standard approaches involving chemotherapy with or without hematopoietic stem cell transplantation, and investigational approaches studied in the context of a formal clinical trial, also involving chemotherapy and transplantation. Given the natural history of the illness (as established by Freireich et al in the 1950s and 1960s), it would be difficult to recommend a purely palliative strategy except perhaps in the elderly and/or infirm, as discussed below.

The choice between standard and experimental therapy largely depends on the prognosis following use of the former, and disease prognosis is so variable that it suggests AML is, in fact, several different diseases. This article considers the various prognostic subsets and therapies for AML.

**Standard Therapy for AML**

In the United States today, most AML patients receive standard therapy under the care of their private physician as described in this article. The two phases of standard treatment of AML are induction of a complete remission (CR) and postremission therapy. Terms such as consolidation, maintenance, or intensification often are used in connection with postremission therapy. Consolidation refers to treatment that is only slightly less intense than induction therapy, maintenance therapy is relatively less intense than consolidation, and intensification therapy rivals or surpasses induction in dose intensity.

The goal of therapy is achievement of a CR (< 5% blasts in the marrow, a neutrophil count exceeding 1,000-1,500/µL, and a platelet count greater than 100,000/µL); such a remission generally has been assumed necessary, although not adequate, for prolonged survival. The differences in survival rates between patients who achieve complete remissions and those who do not have been shown to be almost entirely dependent upon the time they spend in CR. This observation suggests that the achievement of CR per se, rather than a difference in inherent prognosis between responders and nonresponders, is paramount.

The disease recurs in the majority of patients who achieve CRs, making it likely that not all of these remissions are a result of the same degree of antileukemic activity. A future clinical challenge will be to distinguish between significant and cosmetic CR, since the latter predicts especially high relapse rates unless therapy is changed. Such distinctions eventually will be made by using polymerase chain reaction (PCR) technology to detect persistent evidence of a presenting cytogenetic abnormality, immunophenotyping to identify persistent aberrant patterns of cell surface antigens, or simple clinical observation based on data suggesting that the longer the time required to achieve CR, the shorter the subsequent CR.

At any rate, once 2 years have elapsed from the onset of CR, the risk of relapse declines precipitously, with this risk continuing to decrease thereafter. Once 3 years have elapsed from the CR date, the likelihood of relapse becomes < 10%, and it is reasonable to consider patients potentially cured at that time.

**Induction Therapy**

Standard induction therapy generally consists of a combination of an anthracycline and cytarabine (ara-C), with the anthracycline often administered for 3 days and ara-C for 7 days (“3 + 7” regimens). Numerous randomized studies have compared the efficacy of the anthracyclines daunorubicin (Cerubidine), mitoxantrone (Novantrone), and idarubicin (Idamycin) when all are given with 7 days of ara-C. In general, most studies, including a large meta-analysis, found idarubicin to be superior, although differences are less apparent in older patients.
Several comments about standard anthracycline regimens should be considered:

- Results may vary if different doses (eg, 60 mg/m², rather than 45 or 50 mg/m², of daunorubicin daily) of the several anthracyclines are used.
- Survival gains among the various anthracyclines are relatively modest (ie, median survivals generally differ by only several months).
- Results from the same treatment regimen (eg, daunorubicin plus ara-C) in several trials at times exceed the differences among other regimens in the same trial.

These observations make it difficult to attach great significance to the choice of anthracycline regimens for untreated AML.

Randomized trials have found essentially the same results regardless of the dose of ara-C (100 or 200 mg/m² daily by continuous infusion for 7 days)[14] or the addition of either thioguanine[15] or etoposide[16] to the 3 + 7 regimen (with the latter finding obtained in the largest related trial conducted to date).

**Postremission Therapy**

Once patients achieve CR, they typically receive several cycles of consolidation or maintenance therapy employing the initial drugs; treatment is then stopped and the patient observed. Current data indicate that some postremission therapy is beneficial, but how much therapy remains unclear, since durations of therapy are 2 years vs 3 months and 16 vs 7 months in supporting studies.[17,18]

Again, several comments may be in order. First, benefits generally relate to disease-free survival rather than to overall survival, and have not been universally noted.[19,20] Second, the reasons for these discrepancies are unclear, but they might reflect the myelosuppression produced by the maintenance, the intensity of the therapy given prior to maintenance, or, given the variability of AML, the particular mix of patients treated. In any event, we will assume that prolonging maintenance with these agents for more than 6 months has relatively little effect on survival, while recognizing that the issue has not been, and is unlikely to be, unequivocally resolved because of other pressing questions.

Other standard approaches to postremission therapy are allogeneic or autologous hematopoietic stem cell transplantations, using cyclophosphamide (Cytoxan, Neosar) plus total-body irradiation or busulfan (Myleran)/cyclophosphamide and high-dose ara-C.

**Results**

On average, standard therapy produces median survival durations of 6 to 12 months and CR rates of approximately 60% to 65%; the median duration of remission is approximately 1 year, with 15% to 20% of the patients potentially cured. However, these results are inherently misleading, because only a minority of patients can be considered to conform to an average. For most patients, outcome is either better or worse than this average, depending on a well-defined set of prognostic factors.

**Factors Predicting Response to Standard Treatment**

In general, AML patients are not cured, because their treatment proves too toxic, leading to death before the antileukemic response can be fully assessed; or the response is inadequate, and they fail to enter CR despite surviving long enough for therapy to be effective; or they relapse after CR is achieved.[21,22] The variables that predict early death differ from those that predict resistant disease.

**Predictors of Early Death**

Not surprisingly, the principal predictors of early death are age and performance status; organ function and the presence of an infection when treatment begins also play a role. Age is often regarded as a binary variable (with patients placed into younger and older groups), although it is clear that age behaves as a numeric rather than a dichotomous variable (ie, no age cut-off separates worse and better prognosis patients: The older the patient, the worse the outcome).[23]

Table 1 illustrates the proportion of AML patients dying in the first 7 weeks after beginning combination chemotherapy at M. D. Anderson Cancer Center, including patients with refractory anemia with excess blasts in transformation (RAEB-t), now classified as AML by the World Health Organization,[24] and excluding patients with acute promyelocytic leukemia (APL). Seven weeks was chosen for the study end point because previous results indicated that the survival of patients who achieve remission after this interval is closer to those who never achieve CR than to patients who achieve CR within the first 7 weeks of starting chemotherapy.[8] This finding suggests that patients dying after the 7-week period have already exhibited therapeutic resistance, and their deaths cannot
be attributed solely to failure of supportive care. The data in Table 1 indicate the profound effect of performance status on early death rate. Although this effect may be mediated by various cytokines (eg, tumor necrosis factor [TNF]-alpha), multivariate analyses continue to confirm the independent prognostic significance of performance status after accounting for such cytokines. Age also remains independently significant after accounting for this variable and for performance status, as suggested by Table 1. The probability of early death could be predicted by the pretreatment levels of bilirubin and creatinine as well as by the presence of an infection.

The general difficulty in recommending standard chemotherapy for the 10% of patients who are primarily bedridden (Zubrod performance status > 2) prior to beginning therapy is apparent in Table 1. Given the high early death rates, a strong case could be made for a purely palliative approach in this patient population if investigational approaches are unavailable. Any investigational approaches obviously should focus on reduction of early mortality, while having plausible anti-AML effects. Ambulatory patients who are older than 64 have a statistically higher early death rate than younger ambulatory patients (\(P = .0001\)). The primary reasons to consider investigational therapy in these older patients are the cytogenetic abnormalities associated with age, the presence of the multidrug-resistance protein MDR1, and a history of abnormal blood counts or an antecedent hematologic disorder before diagnosis of leukemia.

**Patients Resistant to Therapy**

The chief predictor of resistance to therapy is the leukemic cell karyotype. The consensus is that patients can be placed into three distinct prognostic groups based on cytogenetics.[25] Inversions of chromosome 16 (inv(16)) or translocations between the long arms of chromosomes 8 and 21 (t(8;21)) are associated with the best prognoses; monosomies of chromosomes 5 and/or 7 (-5,-7), deletions of the long arms of these chromosomes (5q-,7q-), or complex karyotypes (³ 3 abnormalities) have the worst prognoses; and other karyotypes, including those that are normal, confer intermediate prognoses.

Figure 1 depicts recent M. D. Anderson data for patients who did not experience early death (ie, who survived the first 7 weeks after beginning chemotherapy). The prognostic effect of cytogenetics is readily apparent: median survival durations of approximately 6 months in patients with chromosome 5 and/or 7 abnormalities, 3 years in patients with inv(16) or t(8;21), and 1.2 years in remaining patients. Complete response rates in the three groups were 37% (73/196), 84% (36/43), and 56% (115/205).

Most important, the subsequent survival of the chromosome 5/7 abnormalities group who remained alive at 7 weeks was uninfuenced by age (< or > 65 years with medians of 26 and 31 weeks, respectively) or by the presence of an antecedent hematologic disorder. This finding suggests that current therapies for this group are inadequate—even for younger patients who would not wish to incur a 5% to 10% chance of early death when subsequent outcome was so poor. Clearly, all patients with chromosome 5/7 abnormalities and a performance status < 3 are candidates for new approaches primarily designed to improve antileukemia effects. In contrast, Figure 1 also indicates that for the favorable inv(16)/t(8;21) group it is appropriate to recommend standard approaches because the subsequent survival gains justify the risks of early death in all but a few patients with performance status > 2. The small sample size complicates efforts to define prognostic variability within the inv(16)/t(8;21) group, and any investigational approach should retain substantial elements of current therapy—in particular, use of high-dose ara-C.

**Intermediate-Prognosis Patients**

The large group of patients with intermediate prognoses based on cytogenetics (Figure 1) provides the most difficulty when recommending between standard and investigational approaches. Admittedly, some patients may opt for standard therapy when informed of a median subsequent survival of 14 months if they do not succumb to early death, while others, similarly informed, may choose an investigational approach. Two pieces of information may be useful when assessing this difficult treatment decision.

First, there is documentation that abnormal blood counts occurring more than 6 months before an AML diagnosis imply a worse prognosis. The 93 patients in the intermediate cytogenetic group without such a history who survived at least 7 weeks after beginning induction therapy had a shorter subsequent survival, compared with the 343 patients with no history of myelodysplastic syndrome, with survival probabilities at 3 years of 12% vs 25%, respectively (\(P = .02\)). Likewise, patients with such histories had a shorter disease-free survival in CR, compared with patients without such histories, with disease-free survival probabilities at 3 years of 0% vs 17% (\(P = .03\)).

Second, Southwest Oncology Group (SWOG) data[26] indicate that MDR1 expression is associated
with lower CR rates, particularly in patients over 55 years old—even among patients with de novo AML and/or favorable and intermediate karyotypes (who are comparable to the M. D. Anderson patients with no or short histories of abnormal blood counts). Specifically, CR rates among elderly (over age 55) patients with favorable or intermediate karyotypes were 22/27 (de novo AML, MDR1-negative), 29/56 (de novo AML, MDR1-positive), 4/7 (secondary AML, MDR1-negative), and 2/12 (secondary AML, MDR1-positive). The differing CR rates reflect differences in the frequency of resistant disease rather than differences in the frequency of early death.

The SWOG data indicate that although MDR1 expression is much less frequent in patients under age 55 (35% vs 71% in older patients), it remains predictive of resistant disease, although not as significantly as in older patients. Investigational therapies appear to be appropriate in patients with intermediate-risk cytogenetics who have secondary AML (ie, following chemotherapy for a prior malignancy), a history of an abnormal blood count or antecedent hematologic disorder extending 6 months or more, or MDR1-positive blasts. When both an antecedent hematologic disorder (or secondary AML) and MDR1 expression are present, the case for investigational approaches is particularly compelling.

**Prognostic Factors for Investigational Approaches**

*Table 2* summarizes the prognostic factors for newly diagnosed AML patients in whom investigational approaches are advisable based on the preceding discussion. The emphasis for patients with poor performance status should be on therapies that may reduce the early death rates (> 50%) seen with standard combinations, while having potential anti-AML effects. In other patients, the focus should be on more effective therapies.

The need to obtain cytogenetic information in all newly diagnosed patients is implicit in these recommendations. At M. D. Anderson, we use this information to plan induction therapy, particularly for patients with chromosome 5/7 abnormalities, in whom CR rates are less than or equal to 50%, as noted above. This strategy may not always be feasible, however, because the cytogenetic results may not be available for several weeks. In such cases, the information should be used to guide postremission therapy. In the future, it is likely that information about MDR1 status also will be essential.

**Age as an Independent Variable**

Older age is an important factor in the *Table 2* schema because of its well-known associations with poor performance status, very poor prognosis cytogenetics, an antecedent hematologic disorder, and MDR1 expression. Nonetheless, age exerts effects that are independent of these variables. Over the past 20 years, only one of the seven patients age 80 or older who presented at M. D. Anderson with de novo AML, no antecedent hematologic disorder, a performance status < 3, and a normal karyotype was alive 6 months after beginning therapy. Hence, patients more than 80 years old are clearly candidates for investigational therapies aimed both at reducing early death rates and improving anti-AML efficacy.

It appears reasonable to consider primarily palliative approaches if investigational therapies are unavailable for the patients summarized in *Table 2*. The early death rates are appreciable: > 50% in patients with Zubrod performance status 3 or 4; and in patients age 65 and over, 20% with performance status 0 to 2 (29% if older than age 79) and 73% with a status of 3 or 4.

**Benefits and Risks of High-Dose Ara-C**

Two different approaches may improve therapeutic outcome for patients summarized in *Table 2*: Administration of the high-dose ara-C regimen or use of conventional allogeneic or autologous transplantation (ie, cyclophosphamide/total-body irradiation or busulfan/cyclophosphamide preparative regimen and standard graft-vs-host prophylaxis and therapy).

Four randomized trials have compared higher doses of ara-C (≥ 2 g/m²) with lower doses (100-200 mg/m²), and all noted longer event-free survivals in CR for high-dose ara-C given during induction (the SWOG and the Australian Leukemia Study Group [ALSG] trials)[29,30] or during postremission therapy (the Eastern Cooperative Oncology Group [ECOG] and Cancer and Leukemia Group B [CALGB] trials).[31,32] The benefit is limited to patients under age 60 to 65 years (several studies noted increased mortality or toxicity, particularly neurotoxicity, in older patients)[29,31,32] and to patients whose disease is already ara-C-sensitive. For example, the ALSG results were obtained in de novo AML patients without an antecedent hematologic disorder, and the CALGB results were in patients with inv(16)/t(8;21) AML.[33]

Essentially parallel M. D. Anderson results further suggest that ara-C is the principal curative agent in patients with inv(16)/t(8;21).[34] In contrast, any benefit obtained by patients in the chromosome
5/7 group is controversial.[33,35] Although the answers to this debate may hinge on the particular high-dose ara-C regimen employed, whatever benefit is obtained is relatively small when viewed against these patients’ underlying prognosis.

In AML patients with inv(16)/t(8;21), these data may argue for routine use of high-dose ara-C during postremission therapy (as was done by the CALGB using 3 g/m² every 12 hours on days 1, 3, and 5). However, the British Medical Research Council (MRC) trials have obtained comparable results in inv(16)/t(8;21) AML patients using lower ara-C doses than the CALGB (eg, 1 g/m² twice daily × 3 days). The MRC is planning to randomly assign patients with low- or intermediate-risk AML in CR to two schedules (a 1.5-g/m² schedule and a 3-g/m² schedule), with the two randomizations given twice daily on days 1, 3, and 5.

Pending reliable evaluation by the AML 15 trial of how much therapy is warranted, current data suggest that some high-dose ara-C (at least 1 g/m²/dose twice daily × 3 days) is warranted in the postremission therapy of inv(16)/t(8;21) patients under age 65. In our experience, those rare patients in the inv(16)/t(8;21) group who are age 65 or over have poorer outcomes than younger patients with the same abnormalities, primarily because of early death. Hence, efforts to reduce the doses of ara-C for these patients are probably in order.

Another approach to increasing the intensity of ara-C therapy has involved administration of fludarabine (Fludara) before each ara-C dose[36] because of the relationship (albeit quite incomplete) between formation and retention of ara-CTP (the active metabolite of ara-C) by AML blasts and outcome of therapy; the saturation of ara-CTP formation at plasma ara-C concentrations achieved with doses ≥ 1 g/m² and the ability of F-araATP (the active metabolite of fludarabine) to increase ara-CTP formation when ara-C doses of 0.5 to 2.0 g/m² are used.

A recent report[37] noted that fludarabine/ara-C regimens were associated with lower CR rates, poorer outcome in CR, and shorter survival after accounting for prognosis in comparison with regimens giving similar doses of ara-C (although by continuous rather than bolus infusion, as when fludarabine was used). There was one exception: Patients with inv(16)/t(8;21) AML appeared to benefit from these regimens.

**Transplant vs Chemotherapy**

Discussions about the relative merits of allogeneic or autologous hematopoietic stem cell transplantation vs continued chemotherapy without transplantation in AML patients in first CR have gone on for the past 20 years. As may be surmised, the very fact that these discussions continue indicates that any differences in outcome among these modalities must be relatively small.

Two recent large trials, in Europe[38] and the United States[39], exemplify this dilemma. In both studies, patients under age 55 in first CR with HLA-compatible sibling donors were assigned to receive an allogeneic marrow transplant after one further course of chemotherapy. Patients without a donor were to be randomized between autologous transplant (purged of residual blasts in the US study) and one further course of high-dose ara-C (with daunorubicin in the European study); standard preparative regimens were employed.

The European trial found superior disease-free survival in patients assigned to either type of transplant (allogeneic: 168, autologous: 127) vs chemotherapy (127), but there was no effect on survival. The US study found no differences in disease-free survival and somewhat better overall survival with chemotherapy. The MRC’s AML 10 trial[40] has found no survival advantage from autologous transplantation done in 4- or 5- course randomization (ie, in addition to chemotherapy). With the possible exceptions of patients under age 20[41] (with low transplant-related mortality) and of patients over age 60 (with high mortality following conventional myeloablative regimens), there is no clear advantage to a particular modality for any group.[42] Patients in the inv(16)/t(8;21) subset may do better with chemotherapy; their prognosis following high-dose ara-C is such that hematopoietic stem cell transplantation cannot be recommended.[43]

The recent relapse rates of hematopoietic stem cell transplantation vs chemotherapy obviously depend on the chemotherapy regimen administered. For example, an explanation for the failure to find a benefit from allogeneic transplantation in children is the improvement in chemotherapy for pediatric AML demonstrated by the AML 10 trial.[44] Should allogeneic stem cell transplantation be proposed, ECOG data suggest no advantage to giving consolidation chemotherapy before transplantation.[45]

**Emerging Concepts in Transplantation and Chemotherapy**

New concepts in both transplantation and chemotherapy are emerging for the treatment of AML. These include the use of blood rather than marrow as the source of stem cell transplantation and allogeneic, nonmyeloablative minitransplants that are less toxic than conventional myeloablative
transplant regimens and are chiefly intended to allow engraftment and take advantage of the graft-vs-leukemia effect.[46] These approaches may allow allogeneic transplants to be tolerated by older patients (over age 60) and may permit more transplants to be performed in younger patients. This is a significant benefit because only 60% to 80% of patients with HLA-compatible sibling donors typically receive a stem cell transplant.[38,39,47,48]

It may be appropriate to defer further comparisons of allogeneic stem cell transplantation and chemotherapy until more time has been allowed for both modalities to improve via application of the investigational approaches described in this article. The entry of patients, such as those described in Table 2, into clinical trials investigating new approaches to either modality is more important than whether a patient is given allogeneic stem cell transplantation or chemotherapy. For now, I see no reason to prefer either allogeneic or autologous stem cell transplantation to chemotherapy in first CR. An equally reasoned case can be made for chemotherapy in first CR followed by allogeneic transplantation at first relapse. The one exception is the inv(16)/t(8;21) cytogenetic subset of patients, who should receive chemotherapy.

**New Approaches to AML Chemotherapy**

Recent discoveries of novel targets for anti-AML therapy may make chemotherapy both more rational and more effective. Table 3 provides a partial list of new anti-AML agents that have recently become available, or soon will be available, for clinical trials.

**Agents Targeting Cell Surface Antigens**

**Gemtuzumab**

Gemtuzumab ozogamicin (CMA 676, Mylotarg) consists of the chemotherapeutic enediyne calicheamicin linked to a monoclonal antibody directed against CD33.[49] This cell surface antigen is a therapeutic target because it is expressed on blasts in most cases of AML but is absent from normal hematopoietic stem cells and nonhematopoietic tissues. The drug was recently approved for treatment of relapsed AML in patients over age 60, based on a multicenter phase II trial. We compared outcome in these 128 patients with that in M. D. Anderson patients in untreated first relapse who received various high-dose, ara-C-containing regimens before initiation of gemtuzumab.[50]

As seen in Table 4, the CR rate was higher with the various ara-C-containing regimens, but CRp—the "p" denotes that the platelet count remained below 100,000/µL—was more frequent with gemtuzumab. Survival of CRp patients appears longer than that seen in nonresponders. A multivariate analysis comparing response to gemtuzumab with ara-C-containing salvage therapy indicated that, after accounting for length of first CR, age, and cytogenetics, gemtuzumab was more likely than ara-C to produce CR if the first CR was 3 to 6 months long. The response rate was higher with ara-C if the initial CR was longer.

These results reflected the well-known relationship between response to ara-C and duration of first CR. Gemtuzumab appears to be less influenced by this variable, which suggests that gemtuzumab is qualitatively different from ara-C and that the two may be combined profitably. With this in mind, numerous clinical trials investigating gemtuzumab combined with ara-C-like agents are under way in both untreated and relapsed AML patients. These combinations may be important because neither alternative—gemtuzumab or ara-C—is good therapy in any sense, at least for relapsed AML, as evidenced by the response rates shown in Table 4 and the brevity of many of the remissions.

**HuM195 and Anti-CD45**

HuM195 is another anti-CD 33 monoclonal antibody, developed by Jurcic and colleagues, who reported that the unmodified antibody has activity in APL (see below). HuM195 has been attached to both alpha and beta particle-emitting radioisotopes.[51] The latter produce prolonged myelosuppression; thus, their principal value may be as myeloablative transplant preparative regimens. A trial conducted by Matthews and associates is investigating an I-131 anti-CD45 monoclonal antibody compound in this context.[52]

Radioimmunotherapy with alpha particles could potentially produce more specific leukemia cell kill with less damage to surrounding normal tissues. This reflects their shorter path length. A phase I study of HuM195 conjugated to Bi-213 (as an alpha particle-emitter) rather than to beta-emitters[51] showed that the ratio of radiation delivered to the marrow relative to the whole body was significantly lower than after beta-emitters. These data suggest a role in therapy outside of the transplant setting. The antileukemic activity illustrates the potential future use of alpha particles in the treatment of minimal residual AML, and this application is being investigated by Jurcic et al.

**Agents Targeting MDR1/P-glycoprotein**

New agents assume particular interest when shown to be capable of mediating the therapeutic resistance that unfavorably affects outcome in AML patients.
Cyclosporine

The most unqualified success in reversing high rates of MDR1/P-glycoprotein (PGP) efflux was observed by List with cyclosporine (Neoral, Sandimmune). A randomized SWOG trial found that patients with relapsed AML had significantly better outcome in CR when cyclosporine was given with ara-C and continuous-infusion daunorubicin.[53] Addition of cyclosporine was favorable in both MDR-positive and -negative disease, although the difference was greater in the former setting.

Valspodar

Valspodar (PSC833, Amdray) is a cyclosporine D analog that is 10-fold more effective than cyclosporine in inhibiting MDR1/PGP. It is of particular interest in previously untreated older patients, since MDR1 expression is characteristic of AML in the elderly. Valspodar lacks the renal toxicity of cyclosporine in untreated older patients, but both the CALGB trial[54] and an unpublished SWOG pilot trial (personal communication, T. Chauncey, 2000) conclude that valspodar at the usual dose of 10 mg/kg/d together with ara-C, daunorubicin, and etoposide (CALGB) or ara-C and infusional daunorubicin (SWOG) was more toxic than chemotherapy alone (Table 5).[54,55] Nonetheless, there is still interest in valspodar in younger patients and, based on pilot data,[56] the CALGB is planning to randomize newly diagnosed patients under age 60 to chemotherapy with ara-C, daunorubicin, and etoposide with or without valspodar. One possible explanation for the failure of the ECOG valspodar trial[55] to reproduce the results of the SWOG cyclosporine trial[53] is that some mechanism other than MDR1/PGP inhibition is responsible for the efficacy of cyclosporine. In light of these findings, a new SWOG trial is investigating cyclosporine with ara-C and continuous infusion daunorubicin in older, newly diagnosed patients.

Newer Agents

LY-335979 is a new agent that may be less toxic than valspodar. Unlike valspodar, it does not affect the hepatic metabolism of drugs such as the anthracyclines or etoposide. Other new analogs (eg, VX710, VX853) may reverse other mechanisms such as MRP1 efflux.

Agents Inhibiting bcl-2

Many bcl-2-like proteins are thought to decrease the probability of apoptosis in AML blasts after the administration of chemotherapy.[57] Although it may appear surprising that down-regulation of bcl-2 alone could enhance the effect of chemotherapy, promising results have been reported in lymphoma[58] and melanoma.

Marcucci et al[59] have conducted a phase I trial in AML combining the bcl-2 antisense G3139 (Genasense), given at a fixed dose on days 1 to 10, with fludarabine and ara-C, given at escalating doses on days 6 to 10. The administered G3139 dose achieved the target plasma level; four CRs were observed in 11 patients. Although the sample size is small and the effect of chemotherapy given without the antisense is unclear, the case histories suggest that some of the CRs would not have been predicted to occur with fludarabine/ara-C alone. Future directions for investigation include the combination of G3139 with gemtuzumab for treatment of AML in older patients. Such therapy may produce a lower early death rate than traditional therapies.

Hypomethylating Agents

Decitabine

Hypermethylation of CpG-rich regions of the genome is a physiologic mechanism of gene inactivation that is usurped by leukemia cells, which use it to silence tumor-suppressor genes.[60] Decitabine is chemically related to 5-azacytidine but is a more potent in vitro inducer of demethylation and produces CRs in relapsed AML.[61] However, it remains unclear whether the remissions result from the usual cytotoxicity or, more interestingly, from demethylation.

Unpublished data from M. D. Anderson indicate that hypomethylation appears to plateau at decitabine concentrations far below those achieved in patients given usual doses of the drug. Dose-response investigations by Issa and colleagues using low-dose decitabine will hopefully produce hypomethylation without the myelosuppression that occurs at higher doses. This may permit decitabine to be infused for a longer time with the potential of increasing demethylation. This is another therapy of particular interest in older patients and in those with poor performance status.

Histone Deacetylase Inhibitors

The silencing of gene transcription associated with hypermethylation may be mediated by a histone deacetylase complex (HDAC).[62] Accordingly, combinations of HDAC inhibitors (such as phenylbutyrate and depsipeptide) and other hypomethylating agents (such as decitabine) may be synergistic and are likely to be explored.

Antiangiogenesis Therapy

Recent reports of increased angiogenesis in AML,[63,64] together with increased levels of vascular endothelial growth factor (VEGF), have provoked interest in several proposed mediators of
angiogenesis. Addition of the antiangiogenesis agent thalidomide (Thalomid) to chemotherapy was unsuccessful in the treatment of AML, but more specific antiangiogenesis or anti-VEGF inhibitors may be more successful, including anti-VEGF antibodies and SU5416.

Inhibition of Tyrosine Kinase

In addition to inhibiting the angiogenic process, SU5416 also inhibits an endothelial cell receptor with tyrosine kinase (TK) activity. Other TK inhibitors such as imatinib mesylate (Gleevec) or AG1296, possibly combined with chemotherapy, may be used in the treatment of AML because c-kit expression is common in AML, and both compounds inhibit the TK associated with the c-kit receptor. AG1296 also affects the TK activity of FLT3. This may be important because internal tandem duplications of the FLT3 gene appear to convey a poor prognosis in AML. Tse et al reported that AG1296 blocked the ability of such FLT3 mutations to transform normal cells isolated from AML patients and also suppressed phosphorylation in relevant signaling molecules.

Other Agents

Farnesyl Transferase Inhibitors

Although ras mutations are only inconsistently detectable in AML, it has been proposed that ras may be activated and lead to abnormal proliferation through other genetic alterations in the absence of mutation. If so, inhibition of ras may be useful even in AML patients without ras mutations. To function, ras must be farnesylated, and this observation underlies the development and clinical trials of various farnesyl transferase inhibitors. The most extensive experience in AML has been with the compound R115777. Lancet and colleagues treated approximately 34 relapsed AML patients with R115777, which produced 2 CRs. Several cycles may be required for response. Interestingly, preliminary data have failed to indicate a clear relationship between dose and response or between drug dose and the percentage of farnesyl transferase inhibition. Thus, it is not yet clear whether response to these agents is entirely due to farnesyl transferase inhibition. It is possible that the same patients would have responded to ara-C, for example.

Troxacitabine

Troxacitabine is the first l-nucleoside analog (as opposed to the beta-d configuration) shown to have anticaner activity. Unlike ara-C, it is not a substrate for the deactivating enzyme deoxycytidine deaminase. In a phase I trial, Giles et al observed four CRs in 31 patients with relapsed AML and found rash, mucositis, and a painful hand-foot syndrome to be the dose-limiting toxicities. It remains to be seen whether the same prognostic factors will predict response to both troxacitabine and ara-C in relapsed AML (see below), but trials combining troxacitabine with ara-C, idarubicin, topotecan, and gemtuzumab are in progress.

Treatment of Relapsed or Refractory AML

Relapsed and refractory disease are common problems, and overcoming these treatment failures is essential to improving the outcome of patients with AML. The major predictor of response to reinduction therapy is duration of first CR: The shorter the first CR (including a duration of 0), the poorer the response. Duration of first CR, like age, behaves as a numeric rather than a categoric variable. Patients are often considered as having first CR durations for more than, or less than, 1 year, and those with refractory disease are categorized in the latter group. Salvage therapy produces CR rates of 40% to 60% in patients whose first CR lasted for more than 1 year but only 10% to 15% in those with shorter first CRs. A small fraction (10%) of patients in the former group may be curable without hematopoietic stem cell transplantation; however, such an event would be truly extraordinary in the latter group.

Traditional vs Investigational Therapies

An important question concerns whether patients with relapsed/refractory AML should receive different ara-C-containing regimens than used initially or whether they should instead be entered in trials of new agents. During the 1990s, approximately equal numbers of M. D. Anderson patients with first CR durations less than 1 year received standard (high-dose ara-C) therapy (175 patients) and investigational therapy (168 patients) at first relapse. The CR rate was higher with the standard regimen (11% vs 4%), but survival rates were the same with both therapies. This finding reflects the transiency of the CRs and the higher early death rates in patients given the standard regimens. The data also suggest that it is appropriate to enter these patients in trials of new agents at first relapse. In addition, our experience indicates that although readministration of the initial regimen to newly diagnosed patients not in CR after course 1 of induction therapy produced a 30% CR rate; median
survival duration was only 6 months for 192 patients who did not respond to the regimen's first course. Only six (2%) of the patients are alive at 3 years, suggesting that, in contrast to common practice, these patients may be candidates for newer agents.

Two points could be argued. First, it may be that achieving a CR is the better scenario and that remission rates with salvage therapy in refractory AML would be less than 30%. Therefore, a change in therapy should be made only when the patient is in remission. Second, patients who are nonresponders to the first course of chemotherapy range from those whose marrow never becomes hypoplastic to those who come close to attaining CR. Certainly, use of an investigational regimen is less justifiable in the latter patients.

While admitting the validity of these arguments, I believe it is important to investigate new agents relatively early in the course of AML. Such investigations generally have been done only when patients have not responded to several standard treatments, and restricting testing to worse-prognosis patients may increase the likelihood of negative results. Testing in patients in first remission with short first CRs and in patients with complex cytogenetic abnormalities before treatment or once in CR may be more productive.

The situation is different in patients whose first CR duration exceeds 1 year. In these patients, ara-C-containing regimens rather than investigational therapies produced higher CR rates that translate into longer survival. Initial use of investigational regimens in these patients is difficult to justify unless there is some reasonable expectation that the regimen contains a known active therapy. Thus, M. D. Anderson patients with first CR durations > 1 year receive regimens with the investigational component added (such as fludarabine/ara-C/gemtuzumab or troxacitabine/ara-C) because they are unlikely to have substantial remissions and the duration of the remissions is a function of both the induction and the postremission regimens.

Allogeneic hematopoietic stem cell transplantation often is recommended for patients with relapsed or refractory AML. Although I do not denigrate this practice, I know of no studies that, after accounting for prognosis, compare survival in patients given an allogeneic transplant at first relapse with survival in patients given alternative chemotherapy regimens at the same time. Attempts to produce a CR before stem cell transplantation probably are unproductive (but often are mandated by logistical or medical considerations), making the time from relapse to treatment greater with transplantation than with chemotherapy. The consequent potential for bias favoring transplantation would need to be considered in any comparison between chemotherapy and transplantation.

Treatment of APL

Several developments over the past 30 years have made APL the most curable type of AML. Effective therapy began in the early 1970s with the introduction of the anthracyclines,[75,76] and then improved in the 1980s with the addition of all-trans-retinoic acid (ATRA, Vesanoid) to chemotherapy. Current data suggest that ATRA should be combined with anthracyclines during both induction and postremission therapy.[77] A recently developed intravenous liposomal preparation of ATRA (lipoATRA) is likely to be more effective than the oral form[78] and is awaiting approval by the US Food and Drug Administration.

The major side effect of ATRA is a potentially fatal syndrome (occurring in 25% of patients), characterized by fever and leakage of fluid into the extravascular space that produces fluid retention, effusions, dyspnea, and hypotension.[79] The syndrome is effectively treated with high doses of methylprednisolone or dexamethasone.

Arsenic trioxide (Trisonex) produces CR rates of 80% in relapsed APL and may be more effective than ATRA.[80] It is currently being investigated as part of postremission therapy in newly diagnosed patients. Other agents that appear to be effective in APL are HuM195[81] and gemtuzumab, which is being used with ATRA for therapy in newly diagnosed cases.

Risk Stratification

A stratification system has been developed that distinguishes APL patients at low, intermediate, and high risk.[76] Low-risk patients are those presenting with a white blood cell (WBC) count < 10,000/µL and platelet count > 40,000/µL; a WBC count > 10,000/µL identifies a patient at high risk, while others are at intermediate risk. In low-risk patients, cure rates of more than 80% can be anticipated. These patients may only require four to six courses of postremission therapy (eg, idarubicin plus ATRA), following which PCR tests can be done every 3 months for 1 year, with therapy changed to ATRA or arsenic if the PCR reverts to positivity.[82]

APL patients have benefitted from the development of a PCR test to detect molecular evidence of the characteristic 15/17 translocation that provides a sensitive and highly specific means to predict
relapse.[83-85] Following three cycles of anthracycline-containing postremission therapy, more than 90% of patients should be "PCR negative."

Intermediate-risk patients may require a somewhat longer duration of postremission treatment (eg, 6 to 9 months). High-risk patients have both a higher early death rate from hemorrhage and a higher risk of relapse; the cure rate may be only 50%. These patients may benefit from more intensive postremission therapy or the use of arsenic, HuM195, or gemtuzumab. More frequent PCR testing in CR may be advisable (possibly on a monthly basis).

**Conclusions**

Following a long-term plateau in cure rates, new strategies are evolving for the treatment of AML; APL patients especially have benefitted from new treatments over the past 30 years. Some of these therapies are new concepts, while others complement traditional approaches. In the future, specific attention must be given to prognostic factors that identify subsets of AML patients in whom standard therapy is unlikely to be of benefit.

**References:**


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