Therapeutic Options in the Management of Acute Myelogenous Leukemia in Adults

Ruben A. Saez, MD

Several advances in evaluation and treatment have improved the prognosis of adults with acute myelogenous leukemia.

Background: The treatment of acute myelogenous leukemia has evolved in recent years due to advances in supportive care, the identification of prognostic factors, and the careful evaluation of chemotherapeutic modalities in randomized clinical trials.

Methods: The classification and prognostic features are reviewed, and the results from clinical trials have been evaluated with an emphasis on randomized trials and on both remission induction and postremission phases of management.

Results: The combination of an anthracycline and standard-dose Ara-C form the basis of remission induction. High-dose Ara-C has greater toxicity. For postremission therapy, high-dose Ara-C improves results in those with good risk features or normal cytogenetics. Acute promyelocytic leukemia management includes all-trans-retinoic acid.

Conclusions: Once a patient relapses from a nontransplant approach, high-dose therapy and allogeneic marrow transplantation are considered. Autologous stem cell transplantation cures some patients who do not have a donor.

Introduction

Acute myelogenous leukemia (AML) is the most common subtype of acute leukemia in adults, with a steep increase in incidence after the age of 50.1 As the leukemic process replaces normal hematopoiesis, the clinical management revolves around the manifestations of pancytopenia. Most patients present with fatigue or weakness and evidence of capillary bleeding (petechiae). They rarely present with severe bleeding due to disseminated intravascular coagulation (DIC) as it occurs in acute promyelocytic leukemia (APL). Approximately one fourth of patients present with a severe infection such as cellulitis, pneumonia, or septicemia.

Bone marrow aspiration and biopsy with cytochemical stains, flow cytometry, and cytogenetics are done not only to classify the disorder according to the French-American-British (FAB) group, but also to define prognostic factors. The initial therapy (induction phase) and subsequent therapy (postremission phase) will depend on specific characteristics of the patients’ leukemia.

Classification and Prognosis

AML is classified according to the FAB convention into seven subtypes using morphology and cytochemical stains.3 While some subtypes are associated with a typical clinical scenario such as gum and skin infiltration (M5) and DIC (M3), defining a specific subtype is not critical since the initial treatment is similar in all types (except in APL). Certain FAB subtypes have poor-risk biologic features. Acute monoblastic leukemia (M5) has a poor prognosis due to its association with hyperleucocytosis and abnormalities of chromosome 11; these features are associated with high relapse rates.4 Similarly, minimally differentiated AML (M0) carries a poor prognosis.5 This subset is associated with an early stem cell phenotype (CD34,TdT), coexistence of lymphoid markers (80% for one marker, 48% for two markers), and cytogenetic abnormalities of chromosomes 5, 7, or complex karyotypes. Acute erythroleukemia (M6) is difficult to distinguish from the myelodysplastic syndromes and is characterized by abnormalities of chromosome 5 and 7 in the same frequency as treatment-related AML (t-AML), with poor response to therapy.6

Monoclonal antibodies are useful diagnostic tools in AML and are somewhat helpful as prognostic factors.7,8 The findings of CD34, a marker associated with the hematopoietic stem cell, and MDR1, a marker associated with the multidrug resistance phenotype, confer a poor prognosis. In elderly patients (ie, those older than age 55) with AML, the presence of MDR1 is associated with lower complete remission (CR) rates independently of cytogenetics. Lymphoid markers occur commonly in AML and are usually associated with common cytogenetic groups such as t(8,21), t(15,17), and inv(16).9,10 Except for the poor prognosis associated with CD7, lymphoid markers have no prognostic significance.

Cytogenetic analysis in AML has become the most important tool for prognosis in newly diagnosed patients.11,12 Abnormal karyotypes are found in 55% to 78% of adults, of which half represent a single abnormality. While some abnormalities have a specific association with an FAB subgroup, the opposite is not true. As shown in Table 1, these cytogenetic abnormalities have prognostic significance and define the likelihood of achieving CR and long-term survival based on standard
chemotherapeutic approaches. As occurred in childhood ALL, the prognostic implication of a particular abnormality will also change as therapies improve. Additional chromosome abnormalities (secondary) are commonly present at diagnosis and/or at relapse, but its prognostic significance is unknown. Some abnormalities, such as deletion of a sex chromosome, have no prognostic significance, while others [del 9q with t(8;21)] confer a worse prognosis. Chromosomal abnormalities also provide pathogenetic information regarding the mechanisms of leukemogenesis in addition to prognosis as shown in cases of secondary myelodysplasia (MDS) and AML. Deletions of 5q– and 7q– are seen as consequences of alkylator/radiation exposure, while abnormalities of 11q23 are seen with drugs targeting topoisomerase II. Similarly, t-AML with inv(16) or t(8;21) have similar prognosis as de novo AML with the same karyotypes. Thus, when cytogenetic abnormalities and immunophenotyping are considered, age, leukocyte count, and FAB subgroup have less prognostic significance in the treatment of AML.

### Induction Therapy

The goals of induction are to achieve a CR, to eradicate leukemic cells from the bone marrow, and to normalize peripheral counts. Since almost all patients who do not achieve postremission therapy will relapse, persistent but undetected leukemic cells (subclinical leukemia) remain. In large randomized trials, standard induction therapy -- seven days of cytosine arabinoside (Ara-C) plus three days of an anthracycline (7+3) -- achieves CR in 52% to 72% of patients. Approximately half of the patients who do not achieve CR fail because of resistant disease, and half die of toxicity (infection, hemorrhage, multiorgan failure). Thus, attempts to improve the CR rate may increase the toxic death rate. Attempts to improve on the 7+3 therapy by increasing the Ara-C dose from 100 to 200 mg/m² or by adding 6-thioguanine have been unsuccessful. Similarly, the addition of etoposide to the 7+3 regimen did not improve the CR rate or survival. Regarding the choice of the anthracycline, randomized trials have demonstrated that doxorubicin is more toxic (myelositis) than daunorubicin and that idarubicin is associated with higher CR rates, remission duration, and survival. In vitro studies have shown longer intracellular retention for idarubicin, which translates into more effective growth inhibition of leukemic cells that display the MDR phenotype. The major criticism of these studies is that the dose of daunorubicin in these randomized studies (45 mg/m²) may not be the optimal dose (60 mg/m²). Nevertheless, idarubicin is the anthracycline of choice for induction.

The most recent attempt to improve the CR rate uses high-dose Ara-C (HiDAC - 3 g/m²) during induction. In vitro studies defined a steep dose response curve for cytarabine, which was supported by clinical data from refractory AML. Two randomized trials examined the role of HiDAC in induction for AML. The Australian Leukemia Study Group randomized 301 patients to HiDAC (3 g/m² x 8 doses) vs standard-dose Ara-C (100 mg/m² x 7) in combination with daunorubicin (50 mg/m² x 3) plus etoposide (75 mg/m² x 7). All patients received two courses of standard-dose Ara-C x 5 plus daunorubicin x 2 plus etoposide x 5 as consolidation. While the CR was similar (71% vs 74%), the remission duration was 45 months in the HiDAC arm vs 12 months in the standard-dose arm (P<.0005) (Fig 1 - Please see hard copy of journal for Figure 1). No survival difference was seen between the two arms. Mortality was higher during induction in the HiDAC arm (18% vs the standard-dose arm (11%, P=.09), and overall toxicity was higher. These results suggest that the quality of remission was improved in the HiDAC arm. In the SWOG study, patients were randomized between HiDAC (2 g/m² x 12) vs standard-dose Ara-C (200 mg/m² x 7) in combination with daunorubicin (45 mg/m² x 3). Patients in the HiDAC arm received one identical course for consolidation, while those in the standard arm were randomized between two additional courses vs one course of HiDAC as consolidation. HiDAC during induction did not improve the CR rate or the overall survival but did improve relapse-free survival (33% vs 21%, P=.05). HiDAC was associated with higher mortality and overall toxicity during induction. In addition, the use of one cycle of HiDAC as consolidation was more toxic but no more effective than two cycles of standard-dose Ara-C. Both of these studies show improved remission duration when HiDAC is used during induction (but at a cost of increased toxicity) and no improvement in overall survival. In a novel approach, a trial involving 94 patients added HiDAC (2 g/m² x 6) to the 7+3 regimen, which achieved a high CR (89%) with 9% resistant disease and 2% toxic deaths. These results have not yet been confirmed in a multi-institutional setting.

A number of trials have evaluated the use of hematopoietic growth factors (GM-CSF, G-CSF) as supportive care in the treatment of AML, while others have evaluated their use to enhance chemosensitivity (priming). Most trials showed a reduction in the duration of neutropenia with a variable effect in hospitalization and severe infections, but no consistent improvement in CR, CR duration, or survival was seen. Similarly, there was no evidence of decreased drug resistance when these agents were used as chemo sensizers since they produced no effect on CR or survival. Their role in the treatment of AML remains unclear.

### Postremission Therapy

Randomized studies have shown that chemotherapy, either as low-dose maintenance or as repeat of the induction regimen, improves outcome in comparison to no further therapy. These studies defined two courses of consolidation as the standard postremission treatment, with a cure rate of 20% to 25%. Nonrandomized studies using HiDAC as consolidation suggested improved outcome when results were compared to historic controls. The Eastern Cooperative Oncology Group randomized patients in CR who were not candidates for allogeneic bone marrow transplantation (allo-BMT) due to donor availability or age (>40 years) to 24 months of maintenance with Ara-C plus 6-thioguanine vs one course of HiDAC (3 g/m² x 12) plus amsacrine (100 mg/m² x 3). The event-free survival (EFS) was better in the HiDAC arm (27% vs 16%, P=.068), although the mortality rate was higher in the consolidation arm (21% vs 0%), particularly in older patients. When a subgroup analysis was done in 104 patients younger than 41 years of age, EFS and survival at four years were 42% and 42%, respectively, for allo-BMT, 30% and 43% for HiDAC, and 14% and 19% for maintenance. The differences between allo-BMT and maintenance were statistically significant, but those between allo-BMT and consolidation were not. This trial suffered from small numbers and the fact that maintenance was not the standard postremission therapy for AML. Nevertheless, it confirmed the previous single institution experience of HiDAC as consolidation and challenged the role of allo-BMT as the treatment of choice for AML in first complete remission (CR1).

The most important prospective study defining the role of HiDAC as consolidation was conducted by the Cancer and Leukemia Group B (CALGB). A total of 596 patients who achieved CR were randomized to four courses of three dosage levels of cytarabine as postremission therapy: 100 mg/m² x 5 doses, 400 mg/m² x 5 doses, and 3 g/m² x 6 doses. All patients subsequently received four monthly courses of cytarabine (100 mg/m² x 5) plus daunorubicin (45 mg/m² x 1). Disease-free survival differed by age (worse in those older than age 60) and by treatment group; relative to the 100-mg group, the hazard ratio was 0.67 for the 3-g group and 0.75 for the 400-mg group. For patients age 60 years and younger, the probability of being disease-free at four years was 24% in the 100-mg group, 29% in the 40-mg group, and 44% in the 3-g group (P=0.002) (Fig 2 - Please see hard copy of journal for Figure 2). HiDAC was more toxic than the other arms in terms of hospitalization (71% of courses), neurologic toxicity (12% serious events), and mortality in remission (5%). Patients who were 60 years of age or younger were more likely to receive all four courses of HiDAC (62%) than those older than age 60 (29%). An analysis of this trial by cytogenetic groups showed HiDAC improved the outcome in the favorable and intermediate groups but not in the unfavorable group. By multivariate analysis, leukocyte count, cytogenetic group, Ara-C dosage, and induction cycles (in that order) predicted for overall outcome. This study defined four cycles of HiDAC as the new postremission chemotherapy standard in patients aged 60 years or younger, provided the cytogenetics are intermediate or favorable.

### Allogeneic Bone Marrow Transplantation
Allo-BMT is the most effective antileukemic treatment with cure rates of 50% to 60% in CR1, 25% to 35% in second complete remission (CR2), and 10% to 15% in refractory disease (Fig 3). The mechanisms of cure are twofold: the steep dose-response curve that leukemia cells exhibit with radiation and chemotherapy (alkylating agents) and the graft-vs-leukemia effect (GVL). The existence of a GVL effect is derived from observations of decreased relapse rates in patients who develop graft-vs-host disease (GVHD), increased relapse rates in patients who undergo T-cell depletion, and increased relapse rates in syngeneic (identical twins) transplants. In addition, the administration of donor leukocyte infusions achieves CR in one third of patients with relapsed AML after allo-BMT.

Allo-BMT is the only curative treatment for patients with AML who fail induction (15% to 20%), and thus it is critical that patients and their families undergo HLA typing at diagnosis in case they have resistant disease. Factors that predict relapse after allo-BMT in CR1 include unfavorable cytogenetics and the intensity of GVHD prophylaxis. In CR1, reasonable options are regimens based on busulfan and total body irradiation.

Several randomized trials compared allo-BMT in those with HLA-matched sibling donors vs chemotherapy. In these studies, the cure rate ranged from 40% to 64% with allo-BMT and from 19% to 24% with chemotherapy. Since these trials were conducted before the use of HiDAC as postremission therapy, their current relevance is uncertain. Advances in prevention and treatment of GVHD have not translated into improved outcome due to increased relapsed rates, and more intense preparatory regimens have resulted in increased transplant-related mortality. Thus, the efficacy of allo-BMT in CR1 has not improved. However, promising work is underway using targeted hematopoietic irradiation with 131I-anti-CD45 monoclonal antibody.

Autologous Stem Cell Transplantation

Since only 25% to 30% of patients younger than age 56 are candidates for allo-BMT due to the availability of an HLA-identical sibling donor, alternative stem cell sources are needed. Autologous bone marrow or peripheral blood stem cells (auto-SCT) can rescue patients from high-dose therapy. Since GVHD is avoided, this procedure can be offered to older patients. The efficacy with this procedure is related to the intensity of the preparatory regimen since GVL is not present. A potential risk is tumor contamination of the graft, which contributes to relapse and requires purging techniques. Several small studies have shown disease-free survival of 25% (range = 14% to 52%) for auto-SCT in CR2. Differences in results relate to patient selection and the length of the first remission. Results in CR1 show disease-free survival at four years to be 40% to 55% in nonrandomized studies.

The role of purging to improve the outcome of auto-SCT in AML is complex, and no randomized study has been performed to provide conclusive data. Cells in the graft contribute to relapse, as demonstrated by the elegant work of Brenner and colleagues using neomycin-resistant gene-marking studies. Several studies have used ex vivo (4-hydroperoxycyclophosphamide [4-HC]/mafosfamide, monoclonal antibody) purging, while others have used in vivo (HiDAC pre-stem cell collection) purging. These studies suggest the potential benefit of purging is in patients transplanted early after CR1 (three to six months), but there is no clear advantage for any particular strategy. The effect of purging was evaluated in the Autologous Blood and Marrow Transplant Registry of North America. In a paired analysis, the use of purging decreased late relapses and overall treatment failure for patients in CR1 and CR2.

Overall Postremission Strategy for AML in CR1

The emergence of HiDAC as effective consolidation therapy and the success of auto-SCT with low treatment mortality has challenged the traditional recommendation of allo-BMT in CR1. Allo-BMT and auto-SCT have been compared in prospective fashion or through the international and national registries. For patients in CR1 or CR2, allo-BMT decreases relapse and improves leukemia-free survival at three years with respect to auto-SCT. Zittoun et al recently reported on a trial in which patients in CR1 following a course of standard consolidation were either allocated to allo-BMT if they had a donor or randomized to auto-SCT or HiDAC (2 g/m^2 x 8 doses) plus daunorubicin (45 mg/m^2 x 3). The four-year disease-free survival was highest in allo-BMT (55%), lower in auto-SCT (48%), and lowest in HiDAC (30%). There were no differences in overall survival (allo-BMT was 59%, auto-SCT was 56%, and HiDAC was 46%). It should be noted that HiDAC was 8 (2 g/m^2) doses in this study vs 24 (3 g/m^2) doses given in the CALGB study.

Another option is to explore investigational chemotherapy regimens in well-designed NCI-sponsored trials. An approach for younger patients is to undergo allo-BMT using an alternative donor (3-4/6 family donor or unrelated donor). An analysis of 2,055 transplants reported to the International Bone Marrow Transplant Registry showed that the use of alternative donors increased the treatment-related mortality when compared to the use of sibling-matched transplants, thus resulting in inferior leukemia-free survival. These differences were less prominent with advanced leukemias due to the decreased relapse associated with increased GVHD. Alternative donor transplant would be a reasonable option for induction failures, CR1 with poor cytogenetics, CR2, and refractory disease.

Treatment of Relapsed/Refractory AML

Options are limited if a patient does not achieve an initial CR after two induction attempts and a compatible sibling (HLA-identical or 5/6 family donor) is not available. HiDAC-based chemotherapy, etoposide/ mitoxantrone +/- Ara-C, and fludarabine-based chemotherapy have been explored in this setting with CR rates of 30% to 50% and remission duration of three to four months. As these patients exhibit the MDR phenotype, the use of cyclosporine or quinine in addition to standard induction regimens has been explored in an attempt to reverse drug resistance, with promising results in phase II studies.

Another option is to explore investigational chemotherapy regimens in well-designed NCI-sponsored trials. An approach for younger patients is to undergo allo-BMT using an alternative donor (3-4/6 family donor or unrelated donor). An analysis of 2,055 transplants reported to the International Bone Marrow Transplant Registry showed that the use of alternative donors increased the treatment-related mortality when compared to the use of sibling-matched transplants, thus resulting in inferior leukemia-free survival. These differences were less prominent with advanced leukemias due to the decreased relapse associated with increased GVHD. Alternative donor transplant would be a reasonable option for induction failures, CR1 with poor cytogenetics, CR2, and refractory disease.

The outcome of patients who relapse from CR1 depends on the remission duration. Only 20% of patients whose first remission lasts more than two years will be alive at five years when treated by chemotherapy, in contrast to no survivors when initial remission is shorter. Allo-BMT from a compatible family donor offers the best chance of cure for these patients. For those without a donor, allo-BMT using an alternative donor or auto-SCT are viable options. The former is associated with a high treatment-related mortality and the latter with high relapse rates. If the patient is young and has a good match, alternative donor transplant is the better option, while an older patient with a good-risk leukemia (normal cytogenetics and long remission) would benefit from an auto-SCT. While patients in early relapse might be transplanted without reinduction, most patients will require chemotherapy. The choice of salvage will be dictated by patient- and disease-specific characteristics, but since the CR
rate will be lower than at initial diagnosis, an intensive regimen such as the ones used for induction failures is usually recommended. If an auto-SCT is planned (with or without purging) and the marrow has not been collected previously, a cycle of consolidation is given prior to stem cell collection. This same scenario would apply to the unrelated donor setting due to the time it takes to find a donor and perform the transplant.

Patients whose AML is secondary to previous therapy or to MDS have a poor prognosis due to a low CR rate and short remission duration with few, if any, cures.53 Most patients have detectable clonal abnormalities and usually involve chromosomes 5 and/or 7. Since the CR rate is 35% to 40%, an issue is whether these patients should undergo allo-BMT without prior induction. The tempo of the disease, availability of a donor, and socioeconomic factors will affect this decision. Anderson et al54 reported data on 46 patients with secondary AML who underwent allo-BMT without induction. The five-year disease-free survival was 24%, the relapse rate was 31%, and the nonrelapse mortality rate was 44%. Factors associated with improved outcome included younger age, shorter time from diagnosis to BMT (less nonrelapse mortality), and lower peripheral blast count (lower relapse rate). A nonrandomized comparison with patients with t-AML who underwent induction showed similar overall outcome. Thus, transplantation as soon as this complication is diagnosed, hopefully in the MDS phase, will offer the best chance of cure. Perhaps induction should be reserved for those with high tumor burden, since the relapse rate is more than 50%, and for those who require an unrelated donor search.

Treatment of Acute Promyelocytic Leukemia

Acute promyelocytic leukemia (APL) comprises 10% of AML in adults. APL clinically presents with a bleeding diathesis that is often exacerbated by chemotherapy with an early mortality of 10% to 20%. The mechanisms of bleeding are multiple and include DIC, fibrinolysis, and thrombocytopenia.55,56 APL is characterized by the t(15;17), which fuses the promyelocytic leukemia (PML) gene on chromosome 15 to the retinoic acid receptor alpha gene on chromosome 17 (PML/RARα, proportional), which leads to leukemogenesis. All-trans-retinoic acid (ATRA) mediates granulocytic differentiation leading to CR in the majority of patients with resolution of the bleeding diathesis.57,58 The treatment with ATRA has two drawbacks: (1) patients relapse unless cytotoxic chemotherapy is given after achievement of CR, and (2) the retinoic acid syndrome can result, which can be fatal. A French trial by Fenaux et al59 studied 26 patients treated with ATRA followed by chemotherapy (daunorubicin plus Ara-C x 4 courses), and 25 (96%) achieved CR. The EFS was 77% at 18 months. A randomized study comparing ATRA plus chemotherapy vs chemotherapy alone was terminated early because the EFS at 12 months favored the ATRA arm (79% vs 50%).60 A similar trial was done in the United States by the intergroup mechanism.61 Surprisingly, the induction deaths were similar in both groups since the bleeding deaths in the chemotherapy arm were balanced by deaths secondary to the retinoic acid syndrome in the ATRA arm. The 12-month disease-free survival was 57% in the chemotherapy arm vs 92% in the ATRA arm (P=.0001). Similarly, the use of ATRA during maintenance decreased relapses (16% vs 43%).

The retinoic acid syndrome is manifested by fever, dyspnea, diffuse pulmonary infiltrates, weight gain, edema, and episodic hypotension. It occurs two to 21 days after initiation of ATRA and is associated with renal and hepatic dysfunction often in the setting of a rising leucocyte count (not always).62 Its pathophysiology is related to the expression of cellular adhesion molecules and the release of growth factors and cytokines by leukemic cells upon stimulation by ATRA. Two treatment approaches with good success include the use of chemotherapy once the leucocyte count begins to rise (European), and use of high-dose corticosteroids at the earliest clinical suspicion (MASK).

As most patients are cured with ATRA plus chemotherapy, the use of bone marrow transplant is reserved for relapses. The use of RT-PCR will allow detection of minimal disease and help in deciding when to perform the transplant.

References


