Prognostic Factors in Elderly Patients with AML and the Implications for Treatment

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The outcome of older patients with acute myeloid leukemia (AML) has not improved in the last three decades. These patients are more likely to have comorbid illness, poor performance status, and impaired organ function. These clinical features limit their ability to tolerate intensive cytotoxic chemotherapy and result in greater early mortality. The AML seen in elderly patients is also more likely to have evolved from a prior hematologic disorder, and the leukemic blasts are more likely to have poor-risk structural and numeric cytogenetic abnormalities and expression of multidrug resistance protein (MDR1). These blast features have been associated with greater resistance to therapy. Attempts to improve outcome have generally been unsuccessful. Priming of leukemic blasts with granulocyte colony-stimulating factors during cytarabine therapy, granulocyte colony-stimulating factor support to speed neutrophil recovery following induction therapy, inhibition of the MDR1 p-glycoprotein efflux pump, the use of alternative anthracyclines, and the addition of high-dose cytarabine have all been investigated in the last three decades. Further manipulation of standard cytotoxic chemotherapy alone is unlikely to improve the outcome for the majority of patients with AML. Incorporation of molecularly targeted therapies may prove to be less toxic and/or more efficacious. However, patient selection for clinical trials will continue to confound the interpretation of treatment outcomes on clinical trials of older patients with AML.

Treatment of Older Patients with AML: General Considerations

The incidence of acute myeloid leukemia (AML) increases with advancing age.[1] At age 40 years, there is only 1 case of AML per 100,000, but the annual incidence increases to 15 per 100,000 at age greater than 75 years. The prognosis of patients with AML is directly related to age. A number of patient-specific and leukemia-associated factors are believed to explain the poor outcome of older patients with AML. Older patients are less able to tolerate intensive cytotoxic induction and postremission chemotherapy. They often have comorbid medical illnesses which result in limited cardiac, pulmonary, renal and/or hepatic functional reserve. The elderly also have poor tolerance of systemic bacterial and fungal infection. Poor performance status of patients with AML is associated with worse outcome, predominantly due to early mortality during initial induction chemotherapy. AML in older patients is more likely to have evolved from an antecedent hematologic disorder, such as myelodysplastic syndrome, or to have been induced by prior chemotherapy or radiotherapy. There is also a higher incidence of poor-risk cytogenetic changes and expression of the multidrug resistance protein (MDR1) p-glycoprotein (p-gp), which have been associated with poor outcome. Poor-risk blast karyotypes have been variously defined, but generally include complex structural and numeric cytogenetic changes (greater than 3), del(5q) or -5, del(7q) or -7, translocations of 11q23, inv(3q), t(6;9), t(9;22) and others. The prognostic significance of trisomy 8 as an isolated finding is more controversial.[2,3]

The careful selection of patients with AML for single-institution and multicenter therapeutic trials limits the applicability of published reports to the minority of patients with this disease. Eligibility criteria for clinical trials often have stringent requirements for adequate performance status, organ function, and absence of active infection or another malignancy. Clinical trials may also exclude patients with more refractory disease, such as secondary AML. Given the frequently rapid clinical course of untreated AML, and the time required to screen and register patients for clinical trials, patients in urgent need of therapy, who have a greater chance of early mortality, will be less likely to enter clinical trials. Furthermore, patients with AML with rapidly proliferative disease may not be ideal candidates for trials involving noncytotoxic therapies.

An analysis of 2657 Medicare beneficiaries more than 65 years old with AML may more accurately reflect the true outcome of this population.[4] The mortality was 86% and 94% at 1 and 2 years following the diagnosis, respectively. Only 30% of these patients received any form of intravenous chemotherapy in the 2 years following diagnosis (44% in patients aged 65 to 74 years, 24% in patients aged 75 to 84, and 6% in patients aged 85 and above). The study could not distinguish between intensive induction chemotherapy and palliative therapy. Nevertheless, 89% of all patients required hospitalization, and they spent 31% of their remaining days in either a hospital or skilled nursing facility. The high rate of hospitalization is likely due to the consequences of bone marrow failure caused by AML, even in the absence of cytotoxic chemotherapy. The me-

dian survival was longer among treated patients with AML (7 months versus 1 month). Patients living more than 2 months were more likely to have received chemotherapy (43% vs 15%). The superior outcome of treated, elderly patients with AML is due as much to the efficacy of chemotherapy as the ability of the treating physician to choose patients carefully for therapy.

In fact, the European Organization for the Research and Treatment of Cancer (EORTC) conducted a randomized trial of intensive induction chemotherapy with daunorubicin 30 mg/m^2/day for 3 days, cytarabine 100 mg/m^2/day for 7 days, and vincristine 2 mg versus observation until the time of disease progression followed by palliative therapy with hydroxyurea and subcutaneous cytarabine.[5] All patients were more than 65 years old, but had to have preserved organ function and performance status. The patients who received induction chemotherapy had a higher complete remission (CR) rate (58% vs 0%), lower incidence of early mortality (3/31 vs 18/29 patients), longer median survival (21 weeks vs 11 weeks) and greater chance of survival at 2.5 years (17% vs 0%). However, there was no difference in the number of days that patients were hospitalized. On the other hand, a second randomized trial of patients with *de novo* AML greater than age 65 years did not show a survival advantage of an intensive induction chemotherapy regimen (rubidazone and cytarabine) compared with low-dose cytarabine.[6] Although the CR rate was greater with intensive therapy, early mortality, infectious deaths, number of transfusions, and length of hospitalization were all greater with intensive therapy.

Outcome of Therapy of Older Patients with AML: Prognostic Factors

The clinical features and outcomes of elderly patients with AML have been recently reported. Appelbaum and colleagues compared the outcome of AML patients younger than 56 years old with that of patients aged 56 years and older entered on 5 Southwest Oncology Group (SWOG) clinical trials.[7] Secondary AML accounted for 22% to 24% of the patients age 56 and older. The performance status decreased with advancing age; fewer elderly patients had a performance status score of 0. Conversely, the proportion of patients with performance status score of 2 or 3 increased with advancing age: less than 56 years old, 15%; aged 56 to 65, 24%; aged 66 to 75, 26%; and more than 75 years old, 32%. Expression of the MDR1 protein was detected by immunostaining in 33% of patients less than 56 years old and in 57% to 62% of patients aged 56 years and older. Furthermore, the incidence of poor-risk blast karyotypes increased with age (less than 56 years old, 35%; older than age 75, 51%). Conversely, the incidence of CBF translocations, t(8;21) and inv(16), decreased with advancing age (less than 56 years old, 17%; over age 75 years, 4%). The outcome of patients with AML in terms of CR, overall survival and disease-free survival (DFS) was inversely correlated with advancing age; older patients had a higher risk of resistant disease (**Table 1**).

The two SWOG treatment protocols for patients younger than age 56 included more intensive therapy such as high dose cytarabine. However, it is not clear that incorporation of more intensive therapy will affect the prognosis of elderly AML patients. The Leukemia Program at the M. D. Anderson Cancer Center recently reviewed the outcome of 998 patients age 65 and older with AML and high risk myelodysplastic syndromes treated at their center from 1980 to the present.[8] The median age was 71 years, 20% had high-risk myelodysplastic syndromes, 54% had unfavorable karyotypes, and 33% had received prior chemotherapy for another malignancy. These patients were treated with a variety of regimens, but over 65% of patients received an induction chemotherapy regimen including high dose cytarabine. The CR rate was 45% and 29% died during remission induction therapy. The median survival was only 5.4 months, with 1- and 2- year survival rates of 30% and 16%, respectively.

The German AML HD98-B trial included 361 patients more than 60 years old with either *de novo* (64%) or secondary (33%) AML.[9] Patients were treated with idarubicin, standard dose cytarabine, and etoposide (ICE) with or without all *trans*-retinoic acid (ATRA). Patients in first remission then received 6 doses of cytarabine 0.5 g/m^2 every 12 hours and mitoxantrone 10 mg/m^2/day for 2 days (HAM) with or without ATRA. Patients then received either 1 cycle of intravenous idarubicin and etoposide or up to 12 months of oral maintenance therapy with idarubicin and etoposide. The CR rate was 43%, and median overall survival was 9.9

Table 1. Treatment outcomes of patients treated on SWOG studies S9034 and S9500 (younger than 56 years old) and S9031, S9333, and S0112 (56 years and older).

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y
No. patients	368	246	274	80
Response, no. (%)				
CR	235 (64)	113 (46)	108 (39)	26 (33)
Resistant disease	99 (27)	91 (37)	101 (37)	29 (36)
Median overall survival, mo (95% CI)	18.8 (14.9-22.6)	9.0 (8.1-10.2)	6.9 (5.4-7.7)	3.5 (1.4-6.1)
Median DFS, mo (95% CI)	21.6 (15.8-25.5)	7.4 (6.5-8.8)	8.3 (6.3-10.2)	8.9 (5.8-10.8)

Abbreviations: CI, confidence interval; CR, complete response.

months. The cumulative incidence of relapse and survival were superior with a single intensive cycle of intravenous idarubicin and etoposide consolidation compared with oral idarubicin and etoposide.[10] Median survival from the second randomization was 22 months versus 14 months (P = .04). Myelosuppression was either mild or absent with oral maintenance therapy. However, only 29% of the initial patient population could be randomized after HAM consolidation. Furthermore, only 2 of the 98 randomized patients had high-risk blast karyotypes according to the U.K. Medical Research Council (MRC) definition.[11] Therefore, it is impossible to determine the benefit of idarubicin and etoposide consolidation for the majority of elderly patients.

Cytogenetic risk group also affects the CR rate in elderly patients receiving anthracycline and standard dose cytarabine induction chemotherapy. The Eastern Cooperative Oncology Group (ECOG) investigated the efficacy and toxicity of cytarabine in combination with daunorubicin, idarubicin or mitoxantrone induction chemotherapy for AML patients more than 55 years old.[12] The CR rate was 50% and 30% for patients with intermediate-risk and poor-risk blast karyotypes, respectively. Blast karyotype influenced the CR rate with ICE in the AML HD98-B study.[9] The CR rate was 52% for elderly patients with normal blast karyotype. The CR rate was similar or better for patients with the CBF translocations, isolated +8, and isolated +11. The CR rate was much lower in patients with -5/del(5q) (7% of 54 patients), -7/del(7q) (6% of 49 patients), and complex karyotypes (10% of 61 patients). The lower CR rate in patients with poor-risk karyotypes was due primarily to a higher rate of resistant disease. The MRC AML11 study randomized older patient with AML (median age 66 years, 23% with secondary AML) to receive daunorubicin, cytarabine, and thioguanine; cytarabine, daunorubicin and etoposide; or mitoxantrone and cytarabine induction therapy.[13] The outcome was similar with each of the three induction regimens (DAT, 62% CR; ADE 50% CR; MAC 55% CR). Patients with CBF translocations and t(15;17) had a CR rate of 72% compared with a CR rate of 26% in patients with complex karyotypes with five or more structural and numeric cytogenetic abnormalities.[11] Patients with complex karyotypes had a 56% incidence of resistant AML. Finally, the Cancer and Leukemia Group B (CALGB) analyzed the prognostic significance of pretreatment blast karyotype in 635 AML patients aged 60 years and older.[14] Patients were treated on several different protocols, but all included daunorubicin and cytarabine with or without etoposide. The CR rate was 48.5%, with 31.5% having chemotherapy-resistant AML and 20% dying during induction therapy. The CR rate in patients with normal blast karyotype was 57% compared with 77% in patients with CBF translocations, 38% in patients with -7/del(7q), 22% in patients with -5/del(5q), and 25% in patients with complex karyotypes with more than 3 abnormalities.

Blast karyotype has been shown to affect the prognosis of younger patients with AML in first remission who receive postremission therapy with high-dose cytarabine, autologous hematopoietic stem cell transplantation (HSCT) or family member donor HSCT during first remission.[15-17] The prognostic significance of blast karyotype on DFS and overall survival is less striking in older patients. The survival of patients with poor-risk blast karyotype was only slightly better for patients younger than 56 years old compared with older patients in the SWOG experience, even though the younger patients received more intensive therapy.[7] The survival of patients with CBF translocations was similar in patients younger than 56 years old and those aged 56 to 65. The greatest difference in survival between the younger and older patients with AML treated on SWOG studies was observed in the intermediate karyotypic risk group. The median overall survival of patients more than 55 years old with poor-risk and intermediate-risk blast karyotypes were 4 to 5 months and 7 to 12 months, respectively. Survival at 2 years was identical for patients aged 56 to 64, 65 to 75 and over age 75 years in both the poor-risk and intermediate-risk groups. Pretreatment blast karyotype did predict survival of older patients with AML in the CALGB study 8461.[14] Older patients with AML with core binding factor translocations had a 19.4% 5-year survival compared with 0% for patients with more than 5 cytogenetic abnormalities or rare aberrations.

Expression of the MDR1 protein also correlates with poor response to induction chemotherapy. The CR rate was lower in elderly patients with AML with expression of MDR1 by either an immunophenotypic assay (34% vs 67%) or a functional efflux assay (35% vs 58%).[16] Elderly patients with secondary AML treated on SWOG S9031 also appear to have a worse response to standard induction chemotherapy (24% in secondary AML and 52% in *de novo* AML). A prognostic model for achievement of CR was developed based on the outcome of 234 elderly patients with AML treated with daunorubicin and cytarabine induction therapy on SWOG protocol S9031.[18] Three variables (antecedent hematologic disorder, MDR1 expression and unfavorable risk karyotype) were associated with CR rate: no risk factors, 81% CR; 1 factor, 44% CR; 2 factors, 24% CR; 3 factors, 12% CR.

The M. D. Anderson Cancer Center has identified prognostic factors for CR, 8-week early mortality and overall survival among 998 elderly patients with AML[8] Multivariate analysis found the following factors were predictive of early mortality, CR and overall survival: age more than 75 years, ECOG performance status 2 or higher, unfavorable-risk karyotype, antecedent hematologic disorder 12 months or longer prior to AML diagnosis, creatinine level of 1.3 or higher, and treatment outside of a laminar air flow room. Most patients with AML are not treated in laminar air flow rooms at other centers. If patients had none of these risk factors, the early mortality was 20%, CR rate was 69%, and median survival 16 months. Patients with 2 adverse factors had an 8-week mortality of 36%, a 40% CR rate, and a median survival of 4 months. Finally, patients with 3 or

more adverse factors had a 65% early mortality, 19% CR rate, and median survival of 1 month. Poor performance status was also correlated with inferior outcome due to a greater incidence of early mortality during induction therapy on three SWOG studies of elderly patients.[7]

Molecular analysis of AML blasts has shown the heterogeneity of treatment outcomes of patients with normal blast karyotype can be partially explained by somatic mutation of a number of specific genes, including the receptor tyrosine kinase FLT3, nucleophosmin (NPM), CAATT/enhancer binding protein (C/EBP) alpha, c-KIT and RAS. For example, internal tandem duplication (ITD) of a portion of the juxtamembrane region of FLT3 as well as D835 substitution mutations in the FLT3 tyrosine kinase domain are commonly seen in AML blasts with normal karyotype. The FLT3 ITD and D835 mutations have been associated with a worse prognosis in children and young adults with AML.[19-25] However, it is not clear if these somatic mutations of FLT3 are independent predictors of the prognosis of elderly AML patients. SWOG investigated the impact of FLT3, RAS and p53 mutations on the outcome of 140 elderly patients treated with daunorubicin and cytarabine on SWOG S9031.[26] The FLT3 ITD was detected in 34% of these patients and was associated with higher presenting white blood cell and blast counts and normal blast karyotype, as in other studies. However, in 105 patients with complete cytogenetic and MDR1 data, FLT3 mutational status did not provide any additional prognostic information for achievement of CR after controlling for age, leukocytosis, blast karyotype, and MDR1 expression. FLT3 ITD was associated with a lower risk of resistant disease. These data suggest that the ability of elderly patients to tolerate induction chemotherapy may be the more important factor. The presence of FLT3 ITD did not significantly affect the CR rate, CR duration, or overall survival of patients more than 60 years old treated with high-dose cytarabine–based regimens at M. D. Anderson Cancer Center.[27]

Prior Attempts to Improve Outcome of Older Patients with AML

Granulocyte- and granulocyte-macrophage colony stimulating factors (G-CSF and G-CSF) have been incorporated into the treatment of patients with AML in order to improve outcomes. GM-CSF or placebo was given after completion of daunorubicin and cytarabine induction chemotherapy to patients with AML more than 60 years old (CALGB[28]) or to patients aged 55 to 70 years (ECOG[29]). Although the median duration of grade 4 neutropenia was shorter in both phase 3 studies (CALGB, 2 days; ECOG, 4 days), there was no significant difference in the CR rate. The ECOG study did show a benefit of GM-CSF in terms of lower infection-related mortality. G-CSF or placebo was given beginning on day 8 following daunorubicin and cytarabine induction chemotherapy for patients with AML more than 65 years old.[30] The duration of grade 3 neutropenia was again shorter (21 vs 27 days), but there was no difference in the 8-week mortality (23% vs 27%) or overall survival. However, in this phase 3 study, the CR rate was significantly better in the G-CSF group (70% vs 47%). None of these randomized trials showed a negative effect (e.g., higher rate of resistant disease in patients receiving G-CSF or GM-CSF).

G-CSF has also been used to prime leukemic blasts prior to and during treatment with the cell-cycle–specific drug cytarabine in order to overcome drug resistance. In a randomized trial of younger adult patients with AML aged 18 to 60 years,[31] the administration of G-CSF only during the cytarabine infusion resulted in an improved DFS (42% versus 33% at 4 years). However, there was no difference in CR rate or overall survival, and the benefit was only observed in patients with intermediate-risk blast karyotype. The ECOG evaluated the benefit of GM-CSF priming prior to and during anthracycline and cytarabine induction chemotherapy for patients with AML more than 55 years old.[12] The CR rate and DFS were identical with or without GM-CSF; however, the early mortality was greater in the patients receiving GM-CSF. The EORTC and Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) also investigated the addition of GM-CSF both during and after daunorubicin and cytarabine induction chemotherapy in elderly patients with AML.[32] There was no difference in the CR rate, DFS or overall survival, but the recovery of the neutrophil count was more rapid with GM-CSF. Finally, the EORTC and Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) conducted a randomized study of G-CSF during mitoxantrone, cytarabine and etoposide (MICE) induction chemotherapy in patients with AML older than age 60 years.[33] Patients received G-CSF during MICE, after MICE, both during and after MICE, or neither during nor after MICE. There was no difference in the CR rate, DFS or overall survival between any of these groups. Therefore, it does not appear that priming of leukemic blasts during cytarabine-based induction therapy is beneficial, and it may potentially be harmful in older adult patients.

Anthracyclines and etoposide are substrates for the MDR1 p-gp. An active metabolite of idarubicin, idarubicinol, is known not to be a substrate for p-gp. Since MDR1 expression is greater in older AML patients, idarubicin may be superior to other anthracyclines. Randomized trials of idarubicin versus daunorubicin suggest a benefit of idarubicin in younger patients with AML.[34] The basis of this benefit is not clear, since the two anthracyclines were not compared at biologically equivalent doses. However, the CR rate was not appreciably different in patients older than 60 years in a meta-analysis of several phase 3 studies.[35] There was also no difference in CR rate, DFS and overall survival among patients with AML older than 55 years treated with cytarabine in combination with idarubicin, daunorubicin or mitoxantrone.[12] However, there was a trend for greater early mortality among the idarubicin-treated patients.

A number of studies have examined the use of inhibitors of the MDR1 p-gp during remission induction therapy.

Only a single randomized study has shown a benefit to this approach.[36] Poor-risk patients with AML received continuous infusion daunorubicin and high-dose cytarabine with or without cyclosporine, a p-gp inhibitor. Although there was no difference in CR rate, patients receiving cyclosporine had a better DFS. Inhibitors of p-gp also affect the pharmacokinetics of anthracyclines and etoposide. The doses of anthracycline and etoposide had to be decreased when administered with the more specific MDR1 inhibitor PSC-833 (Valspodar; Novartis) due to mucositis and hepatic toxicity. Patients with AML younger than 60 years old were treated with cytarabine, daunorubicin and etoposide with or without PSC-833 on CALGB study 19808.[37,38] There was no difference in CR rate and overall survival between the two groups. The United Kingdom MRC and HOVON also evaluated the addition of PSC-833 to daunorubicin plus cytarabine induction therapy for patients with AML more than 60 years old.[39] Again, the dose of daunorubicin had to be reduced in the group receiving PSC-833. There was no benefit to MDR modulation in terms of CR rate, event-free survival, DFS and overall survival in this phase 3 study. There was also no apparent benefit to PSC-833 in patients with AML with p-gp–positive blasts. Zosuquidar is a highly selective p-gp inhibitor that does not significantly affect anthracycline clearance. Patients with AML more than 60 years old were treated with daunorubicin 45 mg/m^2/day for 3 days and cytarabine 100 mg/m^2/day for 7 days with or without zosuquidar.[40] There was no significant difference in overall survival in the two groups of patients. There were more patients with poor performance status in the group receiving zosuquidar. Furthermore, the zosuquidar may not have been given in the most efficacious schedule with daunorubicin. Nevertheless, there is currently no convincing evidence that inhibition of p-gp will improve the outcome of elderly patients with AML.

High-dose cytarabine is arguably the most active agent in AML. Unfortunately, the incidence of leukoencephalopathy in older patients treated with high-dose cytarabine limits its usefulness in elderly patients with AML.[41] Administration of fludarabine prior to high-dose cytarabine will increase the level of ara-CTP in leukemic blasts.[42] Older patients can tolerate treatment with fludarabine with cytarabine 1.5 to 2 g/m^2 daily.[43] The HOVON evaluated the efficacy of cytarabine 2 g/m^2/day for 5 days and G-CSF with or without fludarabine (FLAG or AG) in elderly patients with AML and patients with high-risk myelodysplastic syndromes.[44] Eighty-eight percent of patients were more than 60 years old. Although the leukemic blasts were shown to have higher concentrations of ara-CTP in a subset of the FLAG-treated patients, there was no significant difference in the CR rate (71% FLAG versus 65% AG) or overall survival at 2 years (39% alive in FLAG group and 29% alive in AG group).

Finally, the ability to cure patients with AML depends on the administration of postremission chemotherapy. CALGB 8525 randomized patients with AML in first CR between 3 different postremission cytarabine regimens: 100 mg/m^2/day for 5 days, 400 mg/m^2/day for 5 days, and 3 g/m^2 for 6 doses. Older patients with AML had a high rate of serious central nervous system toxicity (32% of 31 patients) and mortality, resulting in the amendment of the study and exclusion of patients more than 60 years old.[41] A subsequent CALGB trial randomized AML patients over age 60 years in first CR to either 4 cycles of cytarabine 100 mg/m^2/day for 5 days or 2 cycles of mitoxantrone 5 mg/m^2/day plus cytarabine 0.5 g/m^2 every 12 hours for 3 days.[45] There was no difference in median DFS in the two groups (11 vs 10 months).

The toxicity of induction therapy often precludes further treatment of elderly patients in first remission. The marginal benefit of any postremission chemotherapy for elderly patients with AML in first CR is questionable. The Leukemia Program at the Cleveland Clinic compared the outcomes of 19 elderly patients with AML in first remission who received 2 cycles of postremission therapy (cytarabine 400 mg/m^2/day for 5 days) with 21 elderly patients in first CR who did not receive any postremission therapy by design of the study.[46] The DFS and overall survival of the two groups of patients did not significantly differ. Therefore, the value of any postremission chemotherapy for elderly patients remains uncertain. It is not unreasonable to withhold standard postremission therapy from patients at high risk of relapse (e.g., poor-risk karyotype, history of myelodysplastic syndromes). These patients should be considered for novel approaches to the treatment of minimal residual disease such as vaccine studies and molecularly targeted agents (e.g., tipifarnib).

Alternative Approaches to the Therapy of Older Patients with AML

Low intensity therapies may be of particular benefit for older patients who are not able to tolerate intensive cytotoxic chemotherapy. The United Kingdom AML 14 trial randomized 217 patients who were felt to be unfit for chemotherapy by their physicians to either 20 mg cytarabine by subcutaneous injection twice daily for 10 consecutive days or hydroxyurea.[47] Despite the low intensity of the therapy, the 30-day mortality was 26%, reflecting the inherently aggressive nature of uncontrolled acute leukemia in this population. The CR rate was higher with low-dose cytarabine than with hydroxyurea (18% vs 1%), but there was no significant difference in resource utilization. Low-dose cytarabine was also associated with a survival benefit, but only in older patients with favorable- and intermediate-risk blast karyotype.

The U.S. Food and Drug Administration (FDA) has approved the DNA methyltransferase inhibitors azacitidine and decitabine for patients with myelodysplastic syndromes. The pivotal phase 3 studies were conducted prior to the new World Health Organization (WHO) definition of AML. A substantial minority of patients entered on these

trials actually had AML by WHO criteria (more than 20% leukemic blasts in the bone marrow or peripheral blood). Complete and partial remissions were seen in these patients.[48] Decitabine 20 mg/m^2/day for 5 days has been used as remission induction therapy for older patients with AML. The CR rate (with or without blood count recovery) was 29%; 3 of 10 patients with a poor-risk blast karyotype also had a CR.[49]

A number of new agents have been recently investigated in older, previously untreated patients with AML. Cloretazine is a novel sulfonylhydrazine alkylating agent given as a single intravenous bolus injection. A phase 2 study of 104 previously untreated patients with AML more than 60 years old (median age, 72 years) has been reported.[50] The overall response rate (CR plus CR with incomplete platelet recovery) was 32%, with a higher response rate seen in patients with *de novo* AML (50%) compared with secondary AML (11%). Patients with poor-risk blast karyotype had a 24% response rate. The efficacy of this agent is continuing to be explored in older patients with *de novo* AML.

Clofarabine is a purine nucleoside analog that has been approved by the FDA for pediatric patients with relapsed and refractory acute lymphoblastic leukemia. This drug was rationally designed to resist inactivation by deamination and phosphorylysis. Clofarabine has been shown to have activity in acute myeloid leukemia as a single agent or in combination with cytarabine.[51-53] A multicenter European trial of single-agent clofarabine for patients with AML more than 65 years old who were not felt to be fit for intensive chemotherapy has been reported.[47] The overall response rate was 48% (44% CR) with a median duration of remission of 6 months. The response rate was 47% in patients with adverse karyotype, 31% in patients in secondary AML, and 49% in patients more than 70 years old. The induction mortality was 21%. Neutropenic sepsis was seen in 26% of patients; acute renal failure and transient hepatic abnormalities were also reported. A larger phase 2 study of single-agent clofarabine in a more precisely defined, older, poor-risk AML patient population will complete enrollment in late 2007.

Patients with AML following an antecedent hematologic disorder and AML due to prior exposure to a leukemogenic agent (i.e., secondary AML) have a particularly poor prognosis. A novel, ATP-independent topoisomerase II inhibitor, amonafide, appeared to have activity in this patient population when administered in combination with cytarabine in a single-institution phase 1 study.[54] This observation led to a multicenter phase 2 study of amonafide 600 mg/m^2/day for 5 days with cytarabine 200 mg/m^2/day for 7 days as remission induction therapy in 88 patients with secondary AML.[55] The CR rate was 40%, but identical in patients younger and older than 60 years (39.4% and 43.6%, respectively). The response rate was also identical in patients with AML due to prior exposure to a leukemogenic agent or secondary to an antecedent hematologic disorder. Based on this encouraging response rate compared with prior reports of standard induction chemotherapy in this patient population, a phase 3 study of either amonafide or daunorubicin in combination with cytarabine for patients with secondary AML was activated in late 2007.

Activating mutations of the RAS proto-oncogene have been described in AML blasts. Since the activity of the RAS protein depends on post-translational farnesylation, a number of inhibitors of farnesyl transferase have been developed in an effort to perturb RAS signaling. The oral farnesyl transferase inhibitor, tipifarnib, has been tested in 158 previously untreated patients with AML.[56] This was clearly a poor-risk group of patients with a median age of 74 years, and with prior myelodysplastic syndrome in 75% and unfavorable blast karyotype in 47%. Fourteen percent achieved a CR with a median duration of remission of 7.3 months. However, there was no correlation of response with RAS mutation status, inhibition of protein farnesylation or activation of other signal transduction molecules in this (or other) studies. Survival was better in patients who achieved a response, but no data are available regarding the further therapy of these patients with chemotherapy. A U.S. Intergroup randomized phase 2 study of two different doses (600 mg versus 300 mg twice daily) and two different schedules (21 consecutive days versus days 1-7 and 15-21) of tipifarnib in older, previously untreated patients with AML has been completed.[57] The response rates in each therapeutic arm were similar and less than 20%.

Challenge of Developing Novel Therapy in Older Patients with AML

Although the survival of patients younger than 55 years old has improved over the last three decades, there has been no change in the overall survival of patients more than 55 years old in the same time period.[58] It is therefore highly improbable that the outcome of the majority of patients with AML will improve unless there is significant change in our approach to this disease. Given the clinical experience of the last 30 years, it is likely that the response to any new cytotoxic chemotherapy regimen will be more closely affected by patient selection (and the known prognostic factors) than the biologic effect of the agent. Although a number of newer cytotoxic chemotherapy agents are being developed in elderly patients for whom standard chemotherapy is not felt to be beneficial, the exact definition of this population for the purpose of drug development remains problematic.

Molecularly targeted therapies may ultimately overcome the poor prognosis associated with specific cytogenetic abnormalities or somatic mutations. Nonetheless, even if molecularly targeted therapies are developed for AML, patients will remain at risk of early mortality due to the infectious and hemorrhagic consequences of severe bone marrow failure. Early mortality will be influenced by patient-specific factors such as age, performance status, comorbid illness, vital organ function, and duration of myelosuppression. The very definition of CR in AML, and the

nature of the disease in older patients, will affect the apparent benefit of any novel approach. CR requires both normalization of the marrow blast percentage and reconstitution of normal hematopoiesis with recovery of blood counts. However, elderly patients have decreased bone marrow reserve and often have an antecedent bone marrow stem cell disorder such as myelodysplastic syndrome (either recognized or not). Unless the tested agent also has the ability to repair the underlying bone marrow failure syndrome, or advances in supportive care allow older patients to tolerate severe myelosuppression better, the activity of a novel agent for patients with AML may be underestimated. Achievement of CR does improve survival of patients with AML. On the other hand, morphologic clearance of AML blasts without reconstitution of normal hematopoiesis has not been shown to improve overall survival of AML patients.

It is possible that morphologic clearance of AML may facilitate allogeneic hematopoietic stem cell transplantation (HSCT) as a postremission therapy, i.e., a bridge to transplant.[59] Phase 2 data support the use of allogeneic HSCT with a nonmyeloablative, reduced-intensity conditioning regimen for elderly patients with AML in first CR.[60] However, the applicability of this postremission therapy to older patients remains to be seen. A total of 259 previously untreated patients with AML more than 50 years old were prospectively followed at M. D. Anderson Cancer Center.[61] These patients were mostly treated with high-dose cytarabine in combination with idarubicin. Of the 99 patients who achieved CR (38% of registered patients), 53 patients (54% of CR patients) were seen by a consultant from the Bone Marrow Transplant Program. Only 14 of these patients (5% of all registered patients) were able to receive an allogeneic HSCT with a reduced-intensity conditioning regimen and either a sibling or unrelated stem cell donor.

In summary, advanced age is the most important prognostic factor for determining outcome in AML, due to both patient-specific and disease-specific factors. No single approach can be considered the standard of care for these patients. The general health of the older patient will guide the intensity of the therapeutic approach. Given the poor prognosis of older AML patients who receive currently available therapies, treatment of all older patients with AML on clinical trials with appropriate laboratory correlates should be encouraged. In fact, the National Comprehensive Cancer Network AML Practice Guideline does not list standard combinations of an anthracycline and cytarabine as remission induction therapy for any patient aged 60 to 75 years with poor performance status or complex blast karyotypes and any patient older than 75 years.[62] Complete remission has been associated with improved survival of patients with AML even following less-intensive therapies such as tipifarnib[54] and low-dose cytarabine.[45] Unfortunately, the CR rates are very low with these agents in this patient population. If a novel agent demonstrates a significantly improved CR rate in phase 2 study, especially in patients with known poor-risk features (age over 70, antecedent hematologic disorder, poor-risk blast karyotype), phase 3 study may not be possible. The United Kingdom National Cancer Research Institute AML 14 trial[45] demonstrated that physicians will not allow randomization of their older AML patients between two therapeutic interventions of different intensity. Phase 2 study in this situation may have to be sufficient for durg approval.

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