

Non-Transplant Therapy for Older Adults with Acute Myeloid Leukemia

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Key Words

Acute myeloid leukemia, treatment, outcomes, older adults

Abstract

Acute myeloid leukemia is a disease of older adults, with a median age at diagnosis of 68 years. This group represents a high-risk population, because inherent disease characteristics predict for resistance to chemotherapy and advanced age is accompanied by high treatment-related mortality. Standard remission-induction and postremission therapy can result in a median disease-free survival of 10 months and rare long-term survival. Efforts to improve outcomes have not made a major impact on complete remission rates of 40% to 60%, or on overall survival. Newer therapies, divided into aggressive and nonaggressive approaches, focus on targeting the disease biology specific to older adults and on maximizing quality of life. Clinical trials should be considered at every stage of treatment in this group of patients. (*JNCCN* 2006;4:51–56)

Acute myeloid leukemia (AML) is a disease of older adults, commonly defined as people 60 years of age or older.^{1–5} Because the median age at diagnosis of AML is 68 years, it is likely that over half of the estimated 11,960 new diagnoses of AML in the United States in 2005 will occur in older adults.⁶ This translates to a yearly incidence of new AML diagnoses in the United States of 17.6/100,000 for people 65 years of age or older, compared with 1.8/100,000 for people younger than 65 years, and an increase in diagnoses, reported as an annual percentage change, of 2.2% per year for those 65 years and older from 1992 to 2002.⁷

The increase in diagnoses of older adults with AML can be explained by several factors. First, the U.S. population as a whole is aging. The U.S. Census Bureau reports that approximately 35 million U.S. citizens were aged 65 years or older in the year 2000. By the year 2030, that number is expected to more than double to greater than 70 million.⁸ With this increase, the incidence of AML in older adults is also expected to double.

Secondly, the number of cases of secondary AML, or what is commonly a precursor to AML—myelodysplastic syndrome (MDS)—is increasing because of environmental exposures that have occurred in the 20th century, and as a result of late effects of chemotherapy and radiation therapy. For example, the incidence of secondary MDS or AML after busulfan/cytosine and total body irradiation conditioning regimens for bone marrow transplantation for low-grade lymphoma is approximately 1% per year, with no plateau to the curve.⁹ As the numbers of patients treated with alkylating agents, epipodophyllotoxins, and radiation therapy increases, so will the incidence of secondary disease.

Finally, the recognition that abnormal blood counts in older adults may represent an underlying bone marrow disorder, and not just the normal process of aging, has led to greater referrals to hematologists and oncologists, with subsequent diagnoses of AML and MDS. Results from the third National Health and Nutrition Survey, which assessed the prevalence of anemia in people aged 65 and older in the United States, found that approximately one third of anemic subjects (which would translate to 1 million older adults) had unexplained anemia. Of these, 17.2% had macrocytic anemia, thrombocytopenia, or neutropenia, findings that could be consistent with MDS or AML.¹⁰ Case finding within this undiagnosed population will result in continued upward incidence trends.

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Biologic Distinction from Younger AML Patients

Before reviewing therapeutic options in older AML patients, physicians must understand why this population fares worse than younger adults with respect to outcomes, and how this disparity influences treatment discussions. Compared with younger adults, older AML patients have fewer good-risk cytogenetic findings (e.g., the core binding factor [CBF] abnormalities [t(8;21) and abnormalities of chromosome 16] and the t[15;17] that defines acute promyelocytic leukemia), and are more likely to have AML with poor-risk cytogenetics (e.g., abnormalities of chromosomes 5, 7, 8, or complex cytogenetics).^{8,11-14} This fact is not surprising, because the disease for many, if not most, older AML patients arose out of an overt or covert antecedent hematologic disorder, resulting in the cytogenetic overlap with MDS (Table 1).¹⁵ Even when cytogenetic-predicted outcome is confined to the high-risk group of older adults, it is still predictive of survival, with fortunate older adults whose leukemias are typified by a CBF abnormality experiencing 5-year overall survival rates of 20%, compared with 0% for those with poor-risk features.¹⁶

Secondary AML is common in this age group, affecting between one quarter and one half of cases, compared with less than 10% in younger adults.^{13,17,18} This type of AML is less responsive to chemotherapy,

thus contributing to the overall poor outcome for older adults.¹⁹

AML in older adults is also more likely to arise from a more proximal stem cell disorder, indicated by CD34 positivity, and with abnormalities in more than one hematopoietic cell lineage.²⁰⁻²³ This fact, in combination with the likelihood that older adults have reduced proliferative capacities in normal hematopoietic cells, probably contributes to the prolonged cytopenia this population experiences compared with younger adults after remission-induction therapy.²⁴ Additionally, leukemic blasts from older adults have greater expression of genes that mediate drug resistance, such as MDR1, the P-glycoprotein (gp170) chemotherapy efflux pump that one study found to be present in 71% of blasts compared with only 35% of blasts in younger AML patients.²⁵ These factors contribute to this population's poor response to chemotherapy.

Clinical Distinction from Younger AML Patients

Older adults with AML have a poor outcome, regardless of the therapeutic approach selected. Although younger AML patients who receive standard remission induction therapy experience complete remission (CR) rates of 65% to 85%, these rates in older adults are generally 25% lower, ranging from approximately 40% to 60%.^{2,3,26-29} Estimates of CR rates in older adults fall with each additional decade of age, to less than 30% in people 70 years of age or older.^{3,30} As expected, long-term disease-free survival rates (usually defined as being alive and disease-free at 5 years of follow-up), which approach 30% in younger adults, are cut in half for older adults, ranging from 5% to 15%.^{2,31-33} This low chance of durable remission comes at a price of high treatment-related mortality, often quoted as being less than 10% in the younger population compared with 25% to 30% in older adults.

These dismal numbers result from: 1) the biologic factors described previously; 2) intolerance to remission-induction therapy because of comorbid disease; and 3) differential metabolism of induction regimen drugs compared with younger adults, resulting in supratherapeutic drug levels.^{26,34,35} Thus, approximately one half of older adults will leave the hospital in a CR; one in four will leave with persistent disease; and one in four will not leave the hospital alive. For 85%

Table 1 Cytogenetic Overlap of Older Adults with AML and Patients with MDS

Risk Group (as defined by IPSS)	Older AML Patients	MDS Patients
Favorable cytogenetics	60%	70%
del (5q)		
Normal		
del (20q)		
-Y		
Unfavorable cytogenetics	22%	16%
-7		
Complex		
Intermediate cytogenetics	18%	14%

Sources: Data are adapted from Byrd et al.¹², Grimwade et al.¹³, and Greenberg et al.¹⁵

to 95% of older adults, any treatment chosen will be ultimately purely palliative.

Treatment Approaches

In older AML patients, only one randomized study has ever shown a survival advantage of remission-induction therapy over low-dose therapy or best supportive care.³⁶ In this study, the survival advantage was 10 weeks, almost exactly the amount of time required for remission induction and one cycle of consolidation therapy. Although hospitalization for remission-induction therapy does not appear to have a durable impact on quality of life, it does cause a significant, self-limited decrease.³⁷ Given this fact and the poor outcome provided with chemotherapy, the decision regarding aggressiveness of therapy should be left up to patients after an informed discussion that incorporates risk estimates modified to the patient's age, performance status, and comorbidities.

Remission-Induction Therapy

With respect to remission-induction therapy, older and younger AML patients are treated similarly. The core of remission-induction therapy consists of an anthracycline or anthracenedione combined with cytosine arabinoside, a regimen that has changed little since it was first described 30 years ago³⁸ and refined 25 years ago.³⁹ Typically, daunorubicin is given at a dose of 45 mg/m²/d for 3 days, or mitoxantrone or idarubicin is given at doses of 12 mg/m²/d for 3 days, in combination with Ara-C, which is administered as a continuous infusion at 100 or 200 mg/m²/d for 7 days (referred to as 7+3 chemotherapy). Patients who experience CR after this approach have a median disease-free survival of approximately 10 months.

Attempts have been made to improve on this regimen by varying the doses of Ara-C or anthracycline; using one anthracycline or anthracenedione compared with another; adding additional drugs; or using growth factors as priming agents or as supportive care.^{3,26,27,29,31,32,40} Although many of these approaches result in improved CR rates, particularly in phase II studies, often these rates drop in the phase III setting. Even if the improved CR rates are sustained in confirmatory studies, they commonly come at the price of increased treatment-related mortality, thus offsetting any potential survival advantage. Some evidence suggests that, once a decision has been made to initiate remission-induction therapy,

delaying the start of therapy can have a negative impact on outcome.^{3,41}

Postremission Therapy

The only older adults with AML who have experienced long-term disease-free survival have received some form of postremission therapy.^{2-4,32} However, no randomized study has shown that some amount of postremission therapy provides a survival advantage over no postremission therapy in this population. Researchers thus recommend that older AML patients who have an acceptable performance status receive one to two more cycles of Ara-C, either as a single agent or combined with the same anthracycline or anthracenedione administered for remission induction therapy, at the same doses as given initially but for a protracted course (e.g., 5 days of Ara-C combined with 2 days of the anthracycline or anthracenedione). No additional benefit is derived from more intensive postremission therapy, adding other agents, or maintenance therapy.^{2,32,33}

Newer Treatment Approaches

It would be a gross understatement to say there is room for improvement in the treatment of older AML patients. In general, novel therapeutic approaches either try to maximize tumor kill through more aggressive therapy or try milder approaches that provide some evidence of efficacy with lower treatment-related mortality and, presumably, improved quality of life.

Aggressive Therapy

Efforts have been made to target some of the biologic characteristics specific to older adults with AML. One obvious goal would be to overcome resistance to chemotherapy by directing treatment at a chemotherapy efflux pump. Two major studies in older AML patients have now definitively shown, however, that targeting MDR1 overexpression with the drug PSC-833, in combination with anthracycline-based chemotherapy, provides no additional benefit over standard therapy.^{26,42} Cyclosporine, which works by a similar mechanism of action, is being explored on a cooperative group level. Preliminary results using an antisense agent used to target BCL-2 overexpression (an antiapoptosis signal), oblimersen sodium, in combination with standard 7+3 therapy, indicated activity of the combination therapy, with a CR in 14 of 29

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patients. However, follow-up is too limited to draw survival conclusions.⁴³

Gemtuzumab ozogamicin was approved by the Food and Drug Administration for the treatment of relapsed AML in older adults whose leukemic blasts express CD33. CR rates approach 15%, with approximately another 15% of patients experiencing CR with the exception of platelet count recovery (a CRp).⁴⁴ This drug is being studied in combination with standard therapy and as a single agent in the up-front setting.⁴⁵ It should only be used in the nonrelapsed setting as part of a clinical trial.

Older adults are increasingly offered the option of undergoing stem cell transplantation as post-remission therapy. This approach offers the chance of cure, but again at the cost of high treatment-related mortality. Studies are limited to single-institution experiences, often with a mix of hematologic malignancy subtypes. However, these studies have shown the feasibility of nonmyeloablative approaches, with appreciable survival rates at 2 to 3 years of follow-up.^{46,47} Ablative approaches have also been described in this population,⁴⁸ though they may not provide any advantage over nonablative preparative regimens.⁴⁹

Nonaggressive Therapy

Some targeted oral agents have received attention recently as single-agent therapy in AML. This type of therapy is appealing in the older adult population, because it can be started in the outpatient setting and visits to the clinic or hospital can be minimized. Tipifarnib, a farnesyl transferase inhibitor, has been studied in clinical trials in older adults with AML. In a phase II study of 148 evaluable, previously untreated older adults, the CR rate was 18% with single-agent therapy, and the median overall survival was 5.6 months for all patients.⁵⁰ Other oral agents that target activating mutations in the *FLT3* gene have been studied in patients with relapsed or refractory AML.⁵¹ Many of the patients in these trials were older, and although the findings showed a signal of activity, these drugs are more likely to show benefit in combination with cytotoxic therapy.

Another approach has been to accept the premise that AML in older adults represents a final step in a spectrum of bone marrow disorders that starts with MDS and to apply therapies that have been effective in MDS to older adults with AML. These therapies again hold the potential for a modicum of response (although probably lower than that with standard re-

mission-induction therapy), balanced with outpatient treatment. Examples include 5-azacytidine, decitabine, arsenic trioxide, and the combination of all-*trans* retinoic acid and valproic acid.⁵²⁻⁵⁴ However, these drugs should only be used for the treatment of AML within the context of a clinical trial.

Conclusions

Older adults with AML present a treatment challenge. The disease can be aggressive and recalcitrant to therapy, and the population itself can be fragile. Global issues, such as quality of life and days spent in or out of the hospital, should be included in a discussion of treatment options. As established therapies fall short in efficacy, enrollment in a clinical trial should always be considered in the up-front, post-remission, or salvage setting.

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