

Acute Myeloid Leukemia In the Elderly

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Acute myeloid leukemia (AML) is a malignant stem cell disorder characterized by a disruption in hematopoiesis resulting in accumulation of immature or blast cells in the bone marrow and the peripheral blood. This leads to bone marrow failure, severe cytopenias and death if left untreated. The incidence of AML increases with age, with the majority of patients older than age 60.¹ Elderly patients with AML have a particularly poor prognosis.

DEFINITION

In most clinical trials, there is a clear change towards inferior prognosis in patients over age 55. However, with every decade of life beyond age 55, the prognosis decreases further. Hence, the age-demarcation between elderly and non-elderly has been a source of discussion. The National Comprehensive Cancer Network (NCCN) guidelines have used a cutoff of age 60 to define elderly AML.²

CLINICAL PRESENTATION AND DIAGNOSIS

Patients with AML usually present with symptoms related to their cytopenias. They can develop fevers or infections as a result of neutropenia. Anemia can lead to sometimes rapidly progressing weakness and fatigue. Patients may notice petechiae or easy bruising or bleeding due to thrombocytopenia. When they present to their physician with these symptoms or when routine lab work is done (complete blood count), these abnormalities may be identified. Further testing to diagnose AML can include examination of the peripheral blood smear, bone marrow aspirate and biopsy, cytogenetic and molecular analysis, and immunophenotyping.

PROGNOSIS

In general, the five-year survival rate of all patients with AML is between 20-25%. However, in elderly patients the survival is much worse. In some published series, patients between ages of 55-65 years have a 5 year survival of only 9%.

Furthermore, the prognosis also decreases with increasing age: long-term survival is only 7% and 3.5% in age groups 66-75 years and older than 75 years, respectively.^{3,4,5}

The reasons are multiple. Elderly patients frequently cannot tolerate aggressive induction chemotherapy. Some side effects that are especially toxic to elderly patients include severe myelosuppression leading to infections, cardiotoxicity, and nausea/vomiting. They typically have a higher incidence of comorbid illnesses, poor organ reserve and a poor tolerance to infections. Moreover, AML may more frequently arise from an antecedent hematologic disorder such as a myeloproliferative disorder or myelodysplasia, which is always associated with a worse outcome. There is a higher incidence of poor-risk cytogenetics in elderly AML as well as other poor outcome features, such as a higher prevalence of multi-drug resistance proteins.⁵

Prognosis and cytogenetics of AML are tightly linked. Risk stratification can divide patients with AML among three groups: those with favorable, intermediate and unfavorable cytogenetic abnormalities. (Table 1) This stratification also applies to elderly patients with AML. However, within each cytogenetic risk group, the prognosis with standard treatments decreases with increasing age. Furthermore, with increasing age there is an increase in the proportion of patients with unfavorable risk cytogenetics and a decrease in favorable risk cytogenetics. One

study found that the percentage of favorable risk cytogenetics dropped from 17% in patients ages younger than 56 years to 4% in those aged older than 75 years. Moreover, the percentage of patients with unfavorable cytogenetics increased from 35% in those younger than 56 years to 51% of patients older than 75.²

In addition, AML patients with a normal karyotype, who account for the majority of the cases, can make up a heterogeneous group. Molecular genetics have become increasingly utilized in the characterization of patients with normal karyotypes. Three molecular markers of prognostic significance are FLT3, NPM1, and CEBPA. Table 2 summarizes the prognostic relevance of these markers.

TREATMENT

The conventional initial treatment of AML is induction chemotherapy with the 7+3 regimen, which consists of 7 days of continuous intravenous infusion of cytarabine 100mg/m² and 3 days of daunorubicin 45-60 mg/m². There is roughly a 64-70% chance of obtaining a complete remission with this regimen for all patients with AML. However, this success rate declines to roughly 46% in ages 56-65 years, 39% in patients 66-75 years old, and only 33% of patients older than 75 years.^{2,4,6}

Some elderly patients cannot tolerate aggressive induction chemotherapy; however, there is no agreement upon the ideal age for induction chemotherapy in patients with AML. The decision to treat

Table 1. Cytogenetics and risk stratification

	Chromosomal abnormalities
Favorable risk group	t(15;17), t(8;21), inv(16) or t(16;16)
Intermediate risk group	Normal karyotype, t(9;11), del(9q), del(7q), del(20q), -Y, +8, +11, +13, +21
Unfavorable risk group	Complex karyotype, inv(3), t(6;9), t(6;11), t(11;19), del(5q), -5, -7

Table 2. Molecular markers

Marker	Characteristics	Mutation	Prognosis
NPM1	Nucleolar phosphoprotein	Delocalization of protein to the cytoplasm	Favorable prognosis with higher CR rates and lower relapse rates
CEBPA	Transcription factor involved in normal hematopoiesis	Abnormal protein leading to inability to bind to DNA	Favorable prognosis with higher CR rates and lower relapse rates
FLT3	Tyrosine kinase receptor expressed on hematopoietic cells	Activation of the receptor	Unfavorable prognosis with increased relapse risk and decreased overall survival

with induction chemotherapy depends on several factors such as age, frailty, organ function and comorbid illnesses. However, once a patient is deemed ineligible for induction chemotherapy, treatment is focused mainly on supportive measures, such as transfusions when needed and antibiotics for treatable infections. Low doses of oral chemotherapy such as hydroxyurea can reduce the leukemia burden in patients.⁷ Nonetheless, ultimately, these patients will typically die of their leukemia within a matter of weeks to months from their diagnosis.

For those patients who achieve complete remission with induction chemotherapy, post remission therapy can include either consolidation chemotherapy or allogeneic bone marrow transplant in younger, well suited patients who have a match. Any of the standard post-remission therapies improve cure rates for patients with AML. The standard consolidation regimen chemotherapy for younger patients is high-dose cytarabine, but the benefit with this regimen has been noted only in patients younger than 60 years of age. Furthermore, patients over age 60 have a higher incidence of cerebellar toxicity which can be a devastating side effect of this treatment. Therefore, elderly patients may undergo 1-2 cycles of a lesser intense chemotherapy regimen for consolidation. A very reasonable consolidation regimen is to use 5 days of continuous infusion cytarabine and 2 days of daunorubicin 45-60 mg/m². This is typically very well tolerated in elderly patients.^{1,2}

Despite some success with induction and consolidation chemotherapy in elderly patients with AML, the vast majority will relapse within 18 months and die of their disease. Several novel agents are

under review for elderly patients with AML. The classes of new drugs include hypomethylating agents, nucleoside analogs, farnesyltransferase inhibitors and FLT3 inhibitors.

Elderly patients are often unable to tolerate intensive cytotoxic chemotherapy which is required to treat this aggressive malignancy.

Hypomethylating agents

DNA methylation has been known to lead to gene silencing. In AML, DNA methylation causes silencing of tumor suppressor genes. Decitabine is a drug that inhibits DNA methyltransferase, which prevents methylation and thus reactivates the tumor suppressor genes. This agent is currently FDA-approved for the treatment of myelodysplasia. A recent study used decitabine as first line therapy for AML patients older than age 60. Results were promising with an **overall response rate (ORR)** of 25% and a **complete response rate (CR)** of 24%. Further studies are being conducted comparing decitabine with standard therapies.⁸ Azacitidine is another DNA methyltransferase inhibitor. A phase III randomized trial was recently conducted that compared azacitidine with intensive chemotherapy, low-dose cytarabine, or best supportive care. The results showed that azacitidine significantly prolonged

overall survival by 8 months and was better tolerated compared to the other treatments in older patients with less than 25% bon marrow blast count.⁹

Nucleoside analogs

Clofarabine is a second generation purine nucleoside analog. Its mechanism of action is via inhibition of ribonucle-

otide reductase and DNA polymerase. A recent phase II study was conducted using clofarabine as first line treatment of elderly patients older than 60. These patients had one or more unfavorable prognostic factors. The results of the study showed that clofarabine was active against elderly AML patients with an ORR of 46% with 38% CR. This drug was overall relatively well tolerated with the most common side effect of nausea, febrile neutropenia, vomiting, diarrhea, rash, and fatigue.¹⁰

Farnesyltransferase inhibitors

Farnesyltransferase inhibitors are molecules that competitively inhibit farnesyltransferase; several intracellular molecules require farnesylation to function correctly. One particular molecule involved in the pathogenesis of AML is RAS. RAS functions at the plasma membrane to transduce signals to the nucleus from extracellular signals leading to cell growth. Inhibiting farnesylation results in decreased cell proliferation. There have been phase II and phase III studies with tipifarnib. Phase II studies showed a CR rate of 14% and 10% with partial response. The phase III study compared tipifarnib with supportive care and showed only 8% CR for tipifarnib versus 0% for supportive care but no overall survival benefit. However, given the modest activity seen in the phase II trial, using tipifarnib in combination with other chemotherapy drugs is being studied.¹¹

FLT3 tyrosine kinase inhibitors

FLT3 is a receptor tyrosine kinase. Activating mutations lead to proliferation of blast cells. A phase II trial used lestauritnib (CEP701) as first line therapy in previously untreated older

patients ineligible to cytotoxic chemotherapy. Although no patients achieved CR, a clinical response was seen as temporary decrease in bone marrow and peripheral blood blasts. Some patients also became transiently transfusion independent. More studies are continuing with other FLT3 inhibitors as well as in combination with other chemotherapy.¹²

Hematopoietic stem cell transplantation

Many times, stem cell transplant offers another method of treatment for patients with AML. The effectiveness of stem cell transplant is through the graft versus leukemia effect. Patients who develop this phenomenon have a lower risk of relapse. In standard treatment, prior to receiving a stem cell transplant, patients undergo intensive myeloablative chemotherapy. However, the comorbidities and poor performance status of elderly patients often preclude them from getting full intensity chemotherapy.

Recently, reduced intensity chemotherapy regimens have been developed that have reintroduced stem cell transplant into the options that can be offered to elderly patients. Reduced intensity chemotherapy is capable of achieving enough host immunosuppression to allow to engraftment of the transplant without the associated toxic side effects of full intensity chemotherapy.¹³

One issue to consider with elderly patients is the timely identification of a donor. Elderly patients may not have any living, medically suitable siblings for possible donation. This makes this op-

tion less widely available for elderly patients compared to younger AML patients.

CONCLUSION

AML is a hematopoietic disorder that increases in incidence with age. Elderly patients are often unable to tolerate intensive cytotoxic chemotherapy which is required to treat this aggressive malignancy. Its prognosis remains poor. With ongoing clinical trials and new drug development, more options are becoming available in the treatment of elderly patients with AML.

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