Novel Agents for the Treatment of Acute Myeloid Leukemia in the Older Patient

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Abstract
The incidence of acute myeloid leukemia (AML) increases with age, with a median age at diagnosis of 67 years. Older patients have inferior responses to chemotherapy, including not only lower complete remission rates but also short disease-free survival in those who do achieve complete remission. For older patients with a high likelihood of response to chemotherapy, recent data support dose intensification and strong consideration of allogeneic hematopoietic stem cell transplantation. For those unlikely to benefit from chemotherapy because of disease- and/or patient-related factors, novel agents and approaches are being pursued. Agents currently available or under study include the nucleoside analogs clofarabine and sapacitabine, the demethylating agents decitabine and azacitidine, the immunomodulatory agent lenalidomide, and the farnesyl transferase inhibitor tipifarnib. These agents may be administered in the outpatient setting, thus AML in older patients is increasingly becoming an outpatient diagnosis. Additionally, novel agents may prolong survival without inducing complete remissions, and therefore the goals and end points of therapy are also shifting. AML in older patients is a very active current area of investigation. (JNCCN 2011;9:331–335)

Acute Myeloid Leukemia Incidence Increases With Age
The incidence of acute myeloid leukemia (AML) increases with age, with a median age at diagnosis of 67 years. As the proportion of older adults in the population increases, AML in older patients is becoming an increasingly common clinical problem.

Chemotherapy Outcomes in Older Patients
Chemotherapy outcomes, including complete remission rates, disease-free survival, and overall survival, are worse in older patients with AML compared with younger patients. SWOG trials for untreated AML showed complete remission rates of 64%, 46%, 39%, and 33%; median disease-free survival of 21.6, 7.4, 8.3, and 8.9 months; and median overall survival of 18.8, 9.0, 6.9, and 3.5 months in patients aged younger than 56 years, 56 to 65 years, 66 to 75 years, and older than 75 years, respectively. In the MD Anderson experience of 446 intensively treated patients aged 70 years or older, the complete remission rate was 45%; 4- and 8-week mortality was 26% and 36%, respectively; and median overall survival was 4.6 months for 430 patients without core-binding factor (CBF) cytogenetic abnormalities, while for those with CBF abnormalities, the complete remission rate was 63% and median overall survival was 15 months. These data lead to the conclusion that intensive chemotherapy does not benefit most patients aged 70 years or older.

Adverse Prognostic Factors in Older Patients
Adverse prognostic factors that are frequently present in older patients include secondary AML (evolved from myelodysplastic syndromes [MDS] or other antecedent hematologic disorders [AHD], or therapy-related), unfavorable cytogenetic abnormalities (-5/del(5q), -7/del(7q), inv(3), 11q abnormalities, 17p abnormalities or i(17q), del(20q), +13, t(9;22), and complex ≥ 3 ab-
normalities] karyotypes), and overexpression of the multidrug resistance–associated ATP-binding cassette (ABC) protein P-glycoprotein (Pgp, ABCB1), which functions as a drug efflux pump.\(^2,4\) In the SWOG series, the complete remission rate was 81% in patients with none of these factors, and 11% in those with all 3.\(^3\) The importance of ECOG performance status increases with age, as induction death rates were 2%, 18%, 31%, and 50% for patients with a performance status of 2 and were 0%, 29%, 47% and 82% for those with a performance status of 3 at ages younger than 56 years, 56 to 65 years, 66 to 75 years, and older than 75 years, respectively.\(^2\) In the MD Anderson experience, age older than 80 years, complex karyotypes, performance status of 2 to 4, and creatinine greater than 1.3 mg/dL predicted 8-week mortality, with rates of 16%, 31%, 55%, and 71% in patients with 0, 1, 2, or 3 or more of these factors, respectively.\(^3\)

FLT3 internal tandem duplication (ITD), which confers an unfavorable prognosis in younger patients, was recently reported to also be associated with shorter disease-free and overall survival in cytogenetically normal patients with AML aged 60 to 69 years. This report showed a median disease-free survival of 1.0 versus 0.4 years (P < .001) and overall survival of 1.4 versus 0.6 years (P < .001) for wild-type FLT3 versus FLT3-ITD,\(^5\) supporting trials of FLT3 inhibitors in older patients with FLT3-ITD–positive AML.

Disease-free survival is short even for AML with biologically favorable features such as CBF abnormalities,\(^2\) possibly implicating distinct features of leukemogenesis or hematopoietic stem cells in older patients.

**Chemotherapy Dose Intensification**

In a recent comparison of daunorubicin, 90 mg/m\(^2\) versus 45 mg/m\(^2\), in conjunction with cytarabine in 813 patients with AML aged 60 years or older, the higher daunorubicin dose benefited patients aged 60 to 65 years, increasing their complete remission rate from 51% to 73%, and prolonging event-free (29% vs. 14%) and overall survival (38% vs. 23%). Patients with CBF abnormalities in the escalated-dose group also had a higher complete remission rate and a survival advantage, but no other benefit was seen among patients older than 65 years.\(^6\) The ALFA-9801 study compared 80 mg/m\(^2\)/d of daunorubicin given for 3 days, and 12 mg/m\(^2\)/d of idarubicin given for 3 or 4 days in patients aged 50 to 70 years, and found the highest complete remission rate (83%) among patients treated with idarubicin for 3 days, albeit with no difference in event-free or overall survival.\(^7\) One explanation for enhanced efficacy of daunorubicin at 90 mg/m\(^2\) is that this dose might partially overcome Pgp-mediated drug efflux, and idarubicin is known to be less susceptible to Pgp-mediated efflux than daunorubicin.\(^8\)

For older patients whose AML responds to chemotherapy and are eligible for nonmyeloablative allogeneic hematopoietic stem cell transplantation and have donors, this approach shows promise for prolonging disease-free survival.\(^9\)

**Novel Agents**

Therapeutic options for treating AML in older patients are rapidly evolving, and include agents approved by the FDA for the subset of patients with 20% to 30% marrow blasts (azacitidine, decitabine) and for other indications (clofarabine, lenalidomide), those denied approval based on testing but that are still under evaluation (tipifarnib), and those still in early testing (sacibatbine). The novel sulfonilydrazine alkylating agent laromustine (formerly cloretazine) failed to gain FDA approval and is no longer in development, and the immunoconjugate gemtuzumab ozogamicin (Mylotarg) was granted FDA approval in 2000 for treatment of CD33-positive AML in patients aged 60 years or older experiencing first relapse and not considered candidates for other cytotoxic therapies. However, this drug was recently removed from the United States market.

**Clofarabine**

Clofarabine, a second-generation purine nucleoside antimetabolite FDA-approved for the treatment of relapsed and refractory pediatric acute lymphoblastic leukemia, has activity in adult AML, but is not currently FDA-approved for this indication. AML studies to date have used intravenous clofarabine, but oral clofarabine is also now available for study.\(^10\)

In a United States multicenter phase II study,\(^11\) clofarabine, 30 mg/m\(^2\) intravenously daily for 5 days induction, then 20 mg/m\(^2\) reinduction/consolidation, up to 6 cycles, was administered to 112 evaluable patients with untreated AML aged 60 years or older (median age, 71 years). The overall response rate was 46% (38% complete remission and 8% complete remission with incomplete platelet recovery [CRp]) and
30-day mortality was 9.8%. The overall response rate was 39% for those aged 70 years or older and 42% for those with unfavorable karyotypes. Median disease-free survival was 37 weeks, and estimated median overall survival was 41 weeks for all patients and 72 weeks for patients experiencing complete remission.

In 2 European studies, clofarabine was administered to 106 patients with untreated AML who were either older than 70 years, aged 60 to 69 years with poor performance status or cardiac comorbidity, or 65 years or older and unsuitable for intensive chemotherapy. The overall response rate was 48% (32% complete remission, 16% complete remission with incomplete count recovery [CRi]) and 30-day mortality was 18%. Response and overall survival were similar in the unfavorable cytogenetic risk group.

Thus, clofarabine shows encouraging results in older patients, including those with unfavorable karyotypes. However, the treatment is myelosuppressive, with most patients requiring hospitalization for neutropenic fever or infection, thus raising the question of its role compared with standard chemotherapy. A current phase III study compares clofarabine with standard induction chemotherapy in older patients with AML.

Two studies have combined clofarabine with cytarabine in older patients. In one study, clofarabine was administered with cytarabine, 1 g/m²/d, to 60 patients with untreated AML aged 50 years or older. The overall response rate was 60% (52% complete remission, 8% CRp), with 7% induction mortality. Median complete remission duration was 8.1 months, and median overall survival was 10.3 months in all patients and 23.5 months in patients experiencing complete remission. Clofarabine in combination with low-dose cytarabine (20 mg/m² for 14 days) was compared with clofarabine alone in 70 patients with untreated AML aged 60 years or older. The combination arm showed superior complete remission rates (63% vs. 31%; P = .025) and longer event-free survival (7.1 vs. 1.7 months; P = .04), but not overall survival (11.4 vs. 5.8 months; P = .1).

Demethylating Agents
Epigenetic silencing of genes through aberrant DNA methylation represents an attractive therapeutic target in AML and MDS. Two DNA methyltransferase inhibitors, azacitidine and decitabine, were FDA-approved for the treatment of MDS based on trials that included patients with 20% to 30% marrow blasts, which the WHO has redefined as AML. Three CALGB trials of intravenous or subcutaneous azacitidine (75 mg/m²/d for 7 days every 28 days) included 103 patients with AML according to current WHO criteria. Hematologic improvement or better responses were seen in 35% to 48% of patients, with first response after a median of 3 cycles. Median overall survival for 27 patients with AML randomly assigned to azacitidine was 19.3 months compared with 12.9 months for 25 patients assigned to observation. Importantly, azacitidine was continued as long as responses continued. In 113 patients with AML treated in a phase III randomized study comparing azacitidine with conventional care regimens, complete remission rates were similar (18% and 16%, respectively), but median overall survival was 24.5 months for azacitidine-treated patients, compared with 16 months for those treated with conventional care regimens (P = .005), and 2-year survival rates were 50% versus 16% (P = .001).

Several phase II studies have evaluated single-agent decitabine in older patients using different treatment schedules. Among 155 patients treated with decitabine, 135 mg/m², by 72-hour infusion with or without all-trans-retinoic acid (ATRA), the overall response rate (both complete and partial remissions) was 25%, and an antileukemic effect or stable disease occurred in an additional 58%. The median overall survival was 5.5 months. In another study, 55 patients with a mean age of 74 years received decitabine, 20 mg/m²/d, for 5 days every 28 days—a regimen in widespread use for MDS—with an overall response rate of 25% (complete remission, 24%) and stable disease in an additional 29%. Median overall survival was 7.7 months and the 30-day mortality rate 7%. The median number of cycles to complete remission was 4.5. Only 9% of patients with peripheral blood absolute blast count (ABC) 1 to 10 × 10⁹/L, and none of 3 patients with ABC greater than 10 × 10⁹/L experienced a complete remission. In a third phase II study, 53 patients with median age 74 years treated with decitabine, 20 mg/m²/d, for 10 days had a complete remission rate of 47%, with an additional 17% of patients experiencing CRi. Complete remission occurred after a median of 3 cycles. Median disease-free and overall survival was 46 and 55 weeks, respectively, and responses were seen in patients with an initial WBC count of 50 × 10⁹/L or greater. These studies showed efficacy of decitabine in patients with AML with 30% or...
greater marrow blasts, with responses across all risk groups. Randomized studies are ongoing to define the role of demethylating agents in AML.

Histone acetylation is a second mechanism of epigenetic gene silencing in AML cells. Single-agent histone deacetylase inhibitors (HDACi) have had limited activity in MDS and AML, but demethylating agent and HDACi combinations are being explored based on in vitro data suggesting synergy.

**Lenalidomide**

Lenalidomide is an orally administered immunomodulatory agent that is FDA-approved for the treatment of MDS with the del(5q) cytogenetic abnormality. A recently published clinical trial of higher-dose lenalidomide as initial therapy for AML patients older than 60 years with intermediate- or poor-risk karyotypes has shown interesting results. Treatment consisted of 2 courses of lenalidomide at 50 mg/d for 28 days (induction), then 10 mg/d for 12 additional months in patients with no disease progression. CR/CRI occurred in 10 of 33 patients (30%), including 10 of 19 (53%) completing induction. Median complete remission duration was 10 months (range, 1 to ≥ 17 months). Major toxicities were hematologic, but marrow aplasia was not seen on day 15, 28, or 56, and the mechanism of the antileukemic effect remains to be determined. A separate report described 2 elderly patients with AML with trisomy 13 as a sole cytogenetic abnormality who entered morphologic and cytogenetic complete remission with high-dose lenalidomide, one on the trial described earlier and one on another trial. These observations are intriguing and are being further explored.

**Tipifarnib**

Tipifarnib is an orally administered selective inhibitor of farnesyltransferase, an enzyme that catalyzes the addition of a farnesyl moiety to several signaling molecules, including Ras. Activating Ras mutations are present in approximately 15% to 25% of AML cases, and tipifarnib has been tested both as a single agent and with chemotherapy in older patients with AML. In an initial phase II study, tipifarnib given to 158 patients with previously untreated high-risk AML with median age of 74 years produced a complete remission rate of 14% and an overall response rate of 23%. Median complete remission duration was 7.3 months and median overall survival was 5.3 months for all patients, but was 18 months for patients experiencing complete remission. Responses did not correlate with Ras mutation status or inhibition of downstream signaling, but the RASGRP1/APTX gene expression ratio was found to be predictive of response. In a subsequent randomized study in 457 patients with newly diagnosed AML aged 70 years or older, only 8% of those treated with tipifarnib experienced a complete remission and showed no overall survival benefit (median, 107 days) over best supportive care (median, 109 days), and tipifarnib did not gain FDA approval. Tipifarnib in combination with oral etoposide induced complete remission in 21 of 84 patients (25%) older than 70 years with untreated AML, with median complete remission duration of 9.8 months and median overall survival of 22 months for those experiencing complete remission.

**Sapacitabine**

Sapacitabine is a rationally designed, orally administered nucleoside analog that produced a 28% complete remission rate in a phase I trial that included older patients with untreated AML, and is undergoing further testing in this group.

**Novel Concepts**

The lower age limit for eligibility in clinical trials for “older” patients has been variable: 55 years in SWOG trials, 60 years in CALGB trials, and 65 or 70 years in other trials. However, recent data, discussed earlier, seem to suggest that the cutoff for “older” should be 65 or 70 years. In the SWOG analysis, performance status became important at age older than 65 years. Daunorubicin dose escalation benefited patients up to age 65 years, and FLT3-ITD was found to predict outcome in patients up to 69 years. Age is a continuum and also provides incomplete patient-related information in the absence of other factors such as performance status, but, with these caveats, the age cutoff for “older” patients may arguably be 65 or 70 years, rather than 55 or 60 years.

For older patients with a high likelihood of response to chemotherapy, recent data would support dose intensification and strong consideration of transplantation.
Conclusions

For older patients unlikely to benefit from chemotherapy because of disease- and/or patient-related factors, not only are novel agents available, but also treatment approach and goals are changing. Most of the novel agents discussed earlier can be administered in the outpatient setting, and AML in older patients is thus to a significant degree becoming an outpatient diagnosis, except for hospitalizations for complications such as neutropenic fevers and infections. Additionally, agents such as azacitidine seem to prolong survival even in the absence of induction of complete remissions, and the goals and end points of therapy are therefore also shifting.

References