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Editorial

The changing face of acute myeloid leukemia therapeutics in the elderly population

Acute myeloid leukemia (AML) is primarily a disease of the elderly. 66% of patients with newly diagnosed AML in the United States are 65 years and older.[1-3] Elderly patients (≥60–65 years) with AML have a poor prognosis attributable to having disease that is inherently more resistant to current standard cytotoxic agents and/or relatively poor tolerance of these agents.[4-6] Furthermore, elderly patients with AML more frequently have an antecedent hematological disorder, unfavorable cytogenetics, and poorer performance status at presentation[5,7] As a result, despite steady progress in the therapy of AML in younger patients, the treatment of elderly AML has not improved significantly over the last four decades.[3,8,9] The 4–8 weeks mortality with intensive chemotherapy is 30–50% in these patients, and the median survival is 4–7 months.

The poor historical outcomes with intensive chemotherapy have resulted in reluctance by physicians to treat elderly patients with AML. A review of the Surveillance, Epidemiology and End Results and Medicare databases revealed that only 33% of elderly AML patients received leukemia directed treatment.[10] Median overall survival (OS) for the entire group was 2.5 months. Median OS for treated patients was 6 months longer than for untreated patients. Burnett *et al*. reported that low-dose cytarabine (LDAC) was associated with a higher complete remission (CR) rate (18% vs. 1%, $P < 0.001$) and improved OS (estimated 1-year survival rate, 25% vs. 5%; $P < 0.001$) in elderly AML patients[11]. These results highlight the poor outcomes in general, but the potential benefit with leukemia-directed treatment rather than palliation in elderly AML patients, but also the pressing need to develop novel therapeutic strategies better suited for this patient population.[5] A number of these novel agents are currently being evaluated in ongoing clinical trials including the hypomethylating agents (decitabine, azacytidine, SGI-110), purine analogues (clofarabine, cladribine), vosaroxin, CPX351, volasertib, hedgehog inhibitors (PF-04449913, vismodegib), and pracinostat.

Hypomethylating agents are the most frequently used agents in the therapy of elderly AML in the US and Europe.[12] The DACO-016 study compared the efficacy and safety of decitabine (20 mg/m^2/day for 5 days every 4-week) versus investigators choice (including LDAC 20 mg/m^2/day for 10 days every 4-week or best supportive care) in 485 AML patients (median age 73 years) ineligible for cytotoxic chemotherapy.[12,13] The initial analysis showed a trend toward improved survival with decitabine (7.7 vs. 5.0 months; $P = 0.108$) that became significant ($P = 0.037$) with further follow-up. Azacitidine has been explored in elderly patients with AML with 20–30% blasts in a subset analysis of the phase III AZA-001 trial.[14] Elderly AML patients (median age 75 years) were randomized to receive either azacitidine (75 mg/m^2/day for 7 days every 4-week) or conventional care regimen (CCR; best supportive care, LDAC 40 mg/day for 10 days every 4-week or investigators choice).[15] Median OS was 10.4 months (1-year survival 47%) for patients receiving azacitidine compared to 6.5 months (1-year survival 34%) for patients receiving CCR ($P = 0.083$). SGI-110 is a second-generation hypomethylating agent with a longer half-life and more potent hypomethylation than first-generation hypomethylators. In a phase II study SGI-110 a CR rate of 53% was reported in treatment-naïve elderly patients not suitable for intensive chemotherapy.[16]

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Purine analogs have shown encouraging results as single-agents or in combination with LDAC. We have previously demonstrated that the combination of clofarabine and LDAC achieves high response rates with low induction mortality in elderly patients with previously untreated AML.[17] Similarly, cladribine and LDAC alternating with decitabine has been well tolerated with no 4-week mortality, a CR rate of 58%, and a 1-year OS rate of 51%.[18]

A number of novel therapeutic agents are currently being evaluated in elderly patients with AML (>60–65 years). These include volasertib (a Polo-like kinase 1 inhibitor), vosaroxin (a quinolone derivative topoisomerase II inhibitor with reduced cardiotoxocity), CPX351 (a liposomal formulation of cytarabine and daunorubicin at a fixed molar ratio), PF-04449913 (a small molecule inhibitor of the Sonic Hedgehog Pathway) and pracinostat (a pan-histone deacetylase inhibitor). These drugs are currently in phase II/III studies either as single agents or in combination with hypomethylators or LDAC.

In addition to traditional risk factors such as age, cytogenetics, and performance status, factors such as molecular mutations have prognostic and therapeutic impact in AML. A number of mutated or deregulated genes conferring unfavorable (*FLT3-ITD, IDH1/IDH2, WT1, MLL-PTD, TP53, KIT, EVI1, ERG, BAALC*), indeterminate (*NRAS, KRAS, RUNX1, JAK2, TET2, ASXL1, CBL*) or favorable (*NPM1, CEBPA1, GATA2*) prognosis have been identified.[19,20] In addition to their prognostic value, these mutations offer potential therapeutic targets. A number of clinically active agents targeting *FLT3 ITD* and/or *D835* (such as quizartinib, crenolanib and sorafenib), MEK (activated in patients with *NRAS*/*KRAS* mutations) (such as GSK1120212 and MEK-162) and *IDH1/IDH2* (such as ABT199 and AG221) are being investigated in AML. These agents are being used as either single-agents or in combination regimens. In many circumstances, the response rates with such targeted therapies are superior to those achieved with standard therapy with decreased toxicity.

Despite the lack of progress in the past decades that has led to a nihilistic approach to treatment of older patients with AML, significant progress is being made recently in the understanding of the biology and development of therapeutic options that offer a brighter future for this large subset of patients with AML.

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