Therapy for Older AML Patients: The Role of Novel Agents and Allogeneic Stem Cell Transplant

Jeffrey E. Lancet, MD,a and Sergio Giralt, MD,b Tampa, Florida, and Houston, Texas

Abstract

The development of novel therapeutics in acute myeloid leukemia (AML) is driven by the need to improve efficacy and reduce toxicity. Clearly, elderly patients with AML represent a highly heterogeneous group, based on a wide array of disease- and patient-specific characteristics. Therefore, novel treatment strategies aimed at overcoming specific biologic modifiers of disease resistance will be paramount to successful therapy for some, whereas in others, the ability to administer a low-toxicity regimen on a chronic basis to achieve disease control may prove beneficial, perhaps even in the absence of complete responses. In addition, identifying genomic and proteomic expression patterns using an individual's unique neoplastic clone will likely optimize the ability to predict responders to novel therapies and identify new and relevant therapeutic targets. The development of reduced-intensity preparative regimens for allogeneic transplants has allowed physicians and patients to explore the option of long-term disease control. The risk–benefit ratio for this procedure will depend on the disease state, patient performance status, and comorbidities. However, current results underscore that age alone should no longer be a contraindication for allogeneic transplant with curative intent in these patients, and long-term disease control with good quality of life is possible and can be expected. Future trials combining the novel therapies described in this article and novel transplant technologies should allow more elderly patients with AML or myelodysplastic syndromes to experience long and productive lives. (JNCCN 2008;6:1017–1025)

Key Words

Acute myeloid leukemia, allogeneic stem cell transplantation, chemotherapy, targeted therapy, elderly patients

Acute myeloid leukemia (AML) is a clonal disease characterized by proliferation and accumulation of myeloid progenitor cells in the bone marrow, leading ultimately to hematopoietic failure. AML primarily affects older individuals, with a median age of 68 years and a peak incidence of 20 to 25 per 100,000 in people older than 75 years, compared with fewer than 2.5 per 100,000 in people younger than 55 years. Unfortunately, mortality closely parallels the incidence in older individuals, reflecting the high degree of lethality of the disease, despite its relatively low incidence compared with other malignancies.

Historically, treatment outcomes for older individuals with AML have been inferior to those in younger patients. This observation relates to many factors, including unique disease biologic characteristics, comorbidities, poor functional status, and perhaps undertreatment of these patients. The frequency of specific leukemic karyotypes that fall within an unfavorable prognostic subgroup, such as full or partial deletions of chromosomes 5 and 7, t(8;21) abnormalities, and complex karyotypes is higher in elderly patients with AML, as opposed to prognostically favorable cytogenetic abnormalities involving t(15;17), t(8;21), and inversion 16 [t(16;16)], which are rarely encountered in older adults with AML. The presence of multidrug resistance 1 protein (also known as P-glycoprotein [Pgp]) expression in AML is also much more common in elderly AML patients and generally associated with inferior outcomes. Lastly, elderly patients are less tolerant of cytotoxic chemotherapy regimens, as evidenced by induction–mortality rates ranging from 20% to 40%. Such poor tolerance of intensive therapy likely relates to a higher incidence of comorbidities and poor functional status in this patient population.
Given these findings, novel and less-toxic therapeutic approaches are clearly necessary to improve outcomes in elderly patients with AML. The remainder of this article highlights the latest developments of these therapies, including the emerging role of nonmyeloablative allogeneic transplant approaches.

**Novel Therapies**

Great progress has recently been made in the pathobiology of acute leukemias, and these discoveries have been rapidly translated into novel therapies. Although many new therapeutic strategies have focused on the expansion of cytotoxic chemotherapeutics, others have focused on the inhibition of more specific targets within the leukemic clone.

**Novel Chemotherapeutic Compounds**

It is well established, based on prospective clinical trials, that traditional anthracycline-based chemotherapy regimens are highly unsuccessful in providing remission and long-term survival in elderly patients with AML, for many of the reasons indicated previously. In general, complete remission (CR) rates range from 30% to 50%, and 5-year survival averages below 10%. Factors closely associated with worse outcomes in older patients include poor-risk cytogenetics and age of 70 or 75 years or older. The presence of an antecedent hematologic disorder may also contribute to inferior outcomes in older patients. Mortality during induction chemotherapy becomes especially prominent in patients older than 70 years, often approaching 40%.

In response to poor outcomes with traditional cytotoxic agents in this population, large-scale efforts to introduce novel chemotherapeutic drugs and strategies have been undertaken. One observation that may negatively impact chemotherapy success is the overexpression of multidrug-resistant proteins, namely Pgp. Expression of Pgp is especially prevalent within the leukemic blasts of elderly patients with AML, and therefore serves as a potential target for improving chemotherapy outcomes in elderly patients. Unfortunately, most phase III studies have failed to show a beneficial effect of adding Pgp inhibitors to conventional anthracycline-based chemotherapy.

A newer-generation Pgp inhibitor, zosuquidar, is the most potent and selective Pgp inhibitor studied. Early trials using zosuquidar in combination with daunorubicin and cytarabine were recently performed. Preliminary results from an ECOG trial showed no survival benefit in patients treated with zosuquidar using a 6-hour infusion schedule. Alternative dosing schedules of zosuquidar administration are under investigation for maximal inhibition of Pgp function, and preliminary data using a 24-hour continuous infusion schedule of zosuquidar indicated adequate safety and promising early response rates, particularly in patients with Pgp-positive secondary AML.

Other new chemotherapeutic approaches in the elderly are being actively studied. Clofarabine is a novel nucleoside analogue that also inhibits ribonucleotide reductase and is more selectively resistant to intracellular deamination than other agents in the same class. Although extensively studied in acute leukemias, lower-dose clofarabine used as a single agent in elderly patients with AML has garnered recent attention. In a phase II study performed by Burnett et al., elderly patients treated with clofarabine had a CR plus CR with incomplete blood count recovery rate of 46%, including 42% for those patients with adverse cytogenetics. Confirmatory studies in using this single-agent regimen are ongoing.

Another novel chemotherapeutic agent, cloretazine, is a sulfonylhydrazine alkylating agent that is currently undergoing single-agent and combination testing in elderly patients with AML. Preliminary data indicated a 32% CR and CR with incomplete recovery of platelet counts (CRp) rate using single-agent cloretazine in previously untreated AML and high-risk myelodysplastic syndromes (MDS), including a CR/CRp rate of 50% in patients with de-novo AML. These results are being verified in a larger phase II trial.

**Targeted Agents**

Targeted therapeutic approaches in AML hypothetically offer the combined benefits of lower toxicity with unique antileukemic effects. In elderly patients, who have high rates of treatment-related morbidity and mortality and chemoresistance, this approach is justifiable. It is also plausible that targeted therapy will emerge with an eminent role in the postremission/minimal residual disease (MRD) setting, in which leukemia burden is less and a broader, more generalized cytotoxic therapeutic approach would be less desirable. Therefore, larger-scale efforts to identify and screen for markers of MRD in AML will likely help individualize postremission therapies for patients whose leukemia shows unique molecular targets.
Epigenetic Modulators: One promising class of targeted agents in AML is the DNA methyltransferase inhibitors. These agents, although retaining nucleoside analogue–based cytotoxicity properties, potently inhibit DNA promoter methylation, leading to the reversal of gene silencing that may promote leukemic cell survival, growth, and propagation. The agents 5-azacitidine and 5-aza-2’ deoxycytidine (decitabine) have been approved for use in MDS based on results from large phase III clinical trials.20,21

In AML, these agents also seem to have clinical activity, with CR rates ranging from 10% to 20%, but with additional patients experiencing lesser degrees of clinical response (i.e., partial response, hematologic improvement). In addition, early mortality rates using these agents seem to be low, generally less than 10%.22 The absolute benefit and morbidity/mortality rates of these agents compared with standard or best supportive care have not been determined and are the subject of ongoing clinical trials. Combination trials using DNA methyltransferase inhibitors with histone deacetylase inhibitors are also being explored in an attempt to more definitively reverse gene silencing through 2 distinct epigenetic effects.23–25

Another potential therapeutic role for epigenetic modulators in elderly patients with AML may be in the postremission/maintenance setting. Given the good tolerance of these agents and the ability to administer them on a prolonged basis has generated this interest. Recently reported preliminary results of a study using low-dose 5-azacitidine maintenance for patients with AML or MDS in first CR suggested the potential for durable remission durations with this approach.26

Farnesyltransferase Inhibitors: Small molecule inhibitors that target relevant protein or enzymatic activity in cancer are being rapidly developed and deployed. One class of inhibitors includes those known to inhibit intracellular prenylation, namely farnesylation. Farnesyltransferase inhibitors (FTIs) were developed on the premise that mutated ras, being a frequent event in cancer, and whose function is inhabitable with FTIs, was a key target.

Because point mutations or overactivation of ras-related signaling pathways in AML are common events, efforts toward developing FTIs in AML were undertaken. A large phase II trial of the FTI tipifarnib in elderly patients with previously untreated AML showed a CR rate of 14%, extended median survival of 18+ months in patients with CR, and low-rate of hospitalization for treatment-related toxicities.27 Results from a large phase III trial comparing tipifarnib with best supportive care in elderly patients with untreated AML, however, failed to show a survival advantage to FTI therapy.28 The future of FTIs as single agents for untreated AML may depend on genomic identification of patients most likely to respond to and benefit from this treatment.29

Based on a novel mechanism of action and favorable toxicity profile, FTIs have also been explored in the postremission setting. A recent study indicated that tipifarnib, given as maintenance therapy for older AML patients, resulted in a 2-year disease-free survival rate of 30%, which was higher than expected based on historical experience.30 Future studies will hopefully provide more clarity as to the precise role of low-dose maintenance therapy with targeted agents such as these.

FMS-Like Tyrosine Kinase 3 Inhibitors: Inhibitors of FMS-like tyrosine kinase 3 (FLT3) represent another promising class of small molecule–targeted therapies. FLT3 is a receptor tyrosine kinase that is highly and often overexpressed in AML cells and directs various important downstream signaling events that may influence leukemogenesis.31 In up to 30% of AML cases, an internal tandem duplication mutation occurs in the juxtamembrane domain of flt-3, leading to constitutive activation.32 Numerous trials have examined various inhibitors of FLT3, both as single agents and in combination with cytotoxic chemotherapy.12–16 As single agents, FLT3 inhibitors have limited activity, with transient peripheral blood or blast clearance in some patients.33,37 Combination therapy may prove more promising, and phase III trials are at an early stage.

Although not preferentially designed for elderly patients, FLT3 inhibitors, perhaps in combination with cytotoxics, may emerge to become useful when standard chemotherapy frequently fails.

Gemtuzumab Ozogamicin: Gemtuzumab ozogamicin (GO) is a monoclonal antibody against CD33 conjugated to calicheamicin, approved for use in elderly patients with relapsed AML. Combined phase II trial results showed a CR plus CRp rate of 26% in the setting of first relapse, with a median relapse-free survival of 5.2 months.38 Fractionated administration of GO may be associated with less hepatotoxicity without compromising efficacy.39 Some small studies have
also reported on the use of GO for previously untreated AML in elderly patients, both as a single agent and in combination with chemotherapeutics.\(^{40-44}\) As a single agent, CR/CRp rates may vary between 8% and 35%, with higher rates reported in combination, and relatively low rates of early toxic death. Whether this approach is superior to more conventional chemotherapy requires larger and randomized studies.

**Other Targeted Agents:** Several other classes of targeted agents are being developed and tested in early-phase clinical trials. Heat-shock protein inhibitors, phosphatidyl-inositol 3 kinase (PI3K)/Akt pathway inhibitors, Bcl-2 inhibitors, and mitogen-activated protein kinase (MAPK) pathway inhibitors are among the classes of new compounds in early-phase development. These classes of drugs are being considered for trials as single agents and in combination with cytotoxics.

### Allogeneic Stem Cell Transplantation for Older Patients with AML

**Background**

High-dose chemoradiotherapy followed by infusion of autologous or allogeneic bone marrow or peripheral blood is a potentially curative approach for many hematologic malignancies.\(^*\) However, because of toxicity and nonrelapse mortality, allografting with conventional myeloablative conditioning is rarely performed in patients older than 50 years, and autografting in patients older than 65 years is performed in only a few centers. Both single-institution and registry analyses show that older age is associated with a higher incidence of graft-versus-host disease (GVHD) and nonrelapse mortality.\(^{45,46}\) Table 1 summarizes the risks for acute and chronic GVHD and nonrelapse mortality for patients with AML or MDS according to age and donor type, as reported to the 2 largest blood and marrow registries.\(^{47,48}\)

The biologic basis underlying the increased incidence of nonrelapse mortality in older patients is not well understood. In some studies, acute GVHD incidence increases with age.\(^{49}\) GVHD and other transplant complications that result in nonrelapse deaths (i.e., venoocclusive disease and noninfectious pneumonitis) are hypothesized to be partly caused by release of inflammatory cytokines triggered by tissue destruction produced by the preparative regimen.\(^{50}\)

<table>
<thead>
<tr>
<th>Age and Donor Type</th>
<th>IBMTR AML/MDS All Stages Donors (37 teams)</th>
<th>EBMTR (Sibling Transplants for AML in CR1)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grade II–IV Acute GVHD</td>
<td>CGVH Disease</td>
</tr>
<tr>
<td>&lt; 20 y</td>
<td>Sib 5% 22% 23%</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>MUD 11% 46% 29%</td>
<td>46%</td>
</tr>
<tr>
<td>20–45 y</td>
<td>Sib 12% 29% 51%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>MUD 25% 35% 40%</td>
<td>35%</td>
</tr>
<tr>
<td>45 y &gt; 45 y</td>
<td>Sib 16% 24% 51%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>MUD 27% 42% 31%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; CGVH, chronic graft-versus-host disease; CR1, first complete remission; EBMTR, European Bone Marrow Transplant Registry; GVHD, graft-versus-host disease; IBMTR, International Bone Marrow Transplant Registry; MDS, myelodysplastic syndromes; MUD, matched unrelated donors; NRM, nonrelapse mortality; Sib, sibling.

**Rationale**

Improvements in supportive care and the use of peripheral blood stem cells together with improved human leukocyte antigen typing technology have improved transplantation outcomes in younger patients.\(^{51}\) Although some centers have shown that conventional allografting can be successful in patients older than 55 years, the number of these patients who had until recently undergone allografting was extremely small.\(^{52-54}\) From 1995 to 1997, only 23% of the 11,347 patients reported to the International Bone Marrow Transplant Registry and the Autologous Blood and Marrow Transplant Registry were older than 50 years, of which 7% were older than 60.\(^{51}\)

However, AML and MDS are increasingly more common in older patients and, after cytogenetics, age is one of the most important predictors of long-term disease control in AML.\(^{1-3}\) Fewer than 20% of patients with AML who are older than 60 years and who experience a first CR are disease-free at 3 years.\(^{5}\) Thus, new strategies must be developed for this patient population to improve current treatment outcomes. The potency...
The rationale for these approaches was that engraftment of allogeneic progenitor cells could allow exploitation of the graft-versus-malignancy effect, and that less-intensive preparative regimens would be associated with less toxicity, less release of inflammatory cytokines, and therefore less GVHD and lower nonrelapse mortality rates. The advent of less-toxic reduced-intensity regimens has broadened the applicability of allogeneic and autologous transplantation to older and more debilitated patients, as demonstrated by the fact that since 1998, the fraction of patients older than 55 years undergoing allogeneic transplantation has increased significantly and represents one of the largest areas of growth for this procedure (Table 2). Notwithstanding, most patients who undergo allografting are still younger than 70 years, with only 54 patients older than 70 years reported to the registry.

### Current Results With Reduced-Intensity Regimens

Kiss et al. recently reviewed the results of allografting for older patients with AML undergoing RIC allografting. Representative series of RIC allografting for AML or MDS have been summarized in Table 3. In general, 2- to 3-year nonrelapse mortality rates of between 10% and 30% are generally reported, with 3-year event-free survival rates between 30% and 50%. Patients undergoing allograft in first remission have significantly better outcomes with nonrelapse mortality rates of less than 15% and event-free survival rates of 60% at 3 years. Unfortunately, as shown by Estey et al., only a minority of patients experiencing a CR actually undergo allogeneic stem cell transplantation.

### Timing of Stem Cell Transplantation

Considering that the outcome for elderly patients with AML/MDS is so poor, one would think that most patients should undergo transplantation as soon as the diagnosis is made. However, the logistics of finding a donor, plus the poor performance status of many elderly patients with AML/MDS, makes this difficult. Even in patients experiencing a CR, fewer than 15% undergo allografting. Emerging data on the safety and efficacy of this procedure should allow more patients and physicians to consider this a valid option. However, patients with high comorbidity scores and poor performance status continue to have a high rate of transplant-related complications and a 40% 3-year mortality rate, and the risk–benefit ratio must be carefully discussed and addressed with patients and family members before performing this procedure. The lack of a related sibling donor or suitable 10/10 unrelated donor also should not be considered an absolute barrier to proceeding to allograft in elderly patients with AML/MDS, because recent reports from the University of Minnesota have shown the feasibility and efficacy of unrelated donor cord blood transplantation using reduced-intensity regimens in older patients; however, this approach should still be limited to well-designed clinical trials.

### Conclusions

The development of novel therapeutics in AML is driven by the need to improve efficacy and reduce

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**Table 2** Trends in Allograft Recipient Age

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<thead>
<tr>
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<tr>
<td>&lt; 50 y</td>
<td>98%</td>
<td>90%</td>
<td>70%</td>
</tr>
<tr>
<td>50–60 y</td>
<td>2%</td>
<td>9%</td>
<td>20%</td>
</tr>
<tr>
<td>&gt; 60 y</td>
<td>&lt; 1%</td>
<td>1%</td>
<td>10%</td>
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</table>

toxicity. Clearly, elderly patients with AML represent a highly heterogeneous group, based on a wide array of disease- and patient-specific characteristics. Given this heterogeneity, it is not surprising that any individual therapeutic regimen administered to a large number of patients results in a low overall response rate. Therefore, novel treatment strategies aimed at overcoming specific biologic modifiers of disease resistance will be paramount to successful therapy for some, whereas in others the ability to administer a low toxicity regimen on a chronic basis to achieve disease control may prove beneficial, perhaps even in the absence of CRs. In addition, the ability to identify genomic and proteomic expression patterns within an individual’s unique neoplastic clone will likely optimize the ability to predict responders to novel therapies and identify new and relevant therapeutic targets.

The development of reduced-intensity preparative regimens for allogeneic transplantation has allowed physicians and patients to explore the option of long-term disease control. The risk–benefit ratio for this procedure will depend on the disease state, performance status of the patient, and comorbidities. However, current results underscore that age alone should no longer be a contraindication for allogeneic transplant with curative intent in these patients, and long-term disease control with good quality of life is possible and can be expected. Future trials combining the novel therapies described earlier and novel transplant technologies should allow more elderly patients with AML or MDS to experience long and productive lives.

Table 3 Representative Studies of Allogeneic Transplantation for Elderly Patients with AML/MDS or other Hematologic Malignancies

<table>
<thead>
<tr>
<th>Author</th>
<th>N (Median, Age, Range [y])</th>
<th>Regimen</th>
<th>NRM Rates</th>
<th>OS/PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series with AML/MDS only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wong et al.</td>
<td>20 (59, 53–69)</td>
<td>FM/Fb</td>
<td>55% @ 2 y</td>
<td>44%/37% @ 2 y</td>
</tr>
<tr>
<td>De Lima et al.</td>
<td>94 (ns, 27–75)</td>
<td>FM/FAI</td>
<td>FM = 39% @ 3 y</td>
<td>34%/27% @ 3 y</td>
</tr>
<tr>
<td>Gupta et al.</td>
<td>24 (64, 60–71)</td>
<td>F, 200 cGy TBI</td>
<td>25% @ 2 y</td>
<td>52%/44% @ 2 y</td>
</tr>
<tr>
<td>Tauro et al.</td>
<td>76 (52, 18–71)</td>
<td>FM alemtuzumab</td>
<td>19% @ 1 y</td>
<td>41%/37% @ 3 y</td>
</tr>
<tr>
<td>Aoudjane et al.</td>
<td>315 RIC (57, ns) 407 MA (54, ns)</td>
<td>Various RIC and ablative</td>
<td>RIC = 18% @ 2 y</td>
<td>MA = 32% @ 2 y</td>
</tr>
<tr>
<td>Hegenbart et al.</td>
<td>122 (58, 17–74)</td>
<td>F, 200 cGy TBI</td>
<td>16% @ 2 y</td>
<td>&gt; 60 CR1/CR2 48%/42% @ 2 y</td>
</tr>
<tr>
<td>Popat et al.</td>
<td>17 (58, 29–68)</td>
<td>F, 450 cGy TBI</td>
<td>18% @ 1 y</td>
<td>40%/40% @ 2 y</td>
</tr>
<tr>
<td>Kroger et al.</td>
<td>20 (60, 44–70)</td>
<td>F-treosulfan</td>
<td>28% @ 2 y</td>
<td>36%/34% @ 2 y</td>
</tr>
<tr>
<td>Estey et al.</td>
<td>14 (ns, 55–70)</td>
<td>FM</td>
<td>NS</td>
<td>60%/60% @ 2 y</td>
</tr>
<tr>
<td>Series with various hematologic malignancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shimoni et al.</td>
<td>36 (58, 55–66)</td>
<td>Various RIC</td>
<td>39% @ 1 y</td>
<td>52%/43% @ 1 y</td>
</tr>
<tr>
<td>Falda et al.</td>
<td>32 (62, 60–70)</td>
<td>F, 200 cGy TBI</td>
<td>10% @ 1 y</td>
<td>39%/35% @ 2 y</td>
</tr>
<tr>
<td>Majhail et al.</td>
<td>90 (58, 55–70)</td>
<td>Various RIC</td>
<td>MRD 28% @ 0.5 y</td>
<td>UCB 28% @ 0.5 y</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; CR1, first complete remission; CR2, second complete remission; F, fludarabine; FAI, fludarabine, cytarabine, idarubicin; Fb, fludarabine and busulfan; FM, fludarabine and melphalan; MA, myeloablative; MDS, myelodysplastic syndromes; MRD, matched related donor; N, number; NRM, nonrelapse mortality; NS, not significant; OS, overall survival; PFS, progression-free survival; RIC, reduced-intensity conditioning; TBI, total body irradiation; UCB, unrelated cord blood.

References


65. Aoudjhane M, Labopin M, Gorin NC, et al. Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic hematopoietic stem cell transplantation for patients older than 50 years with acute myeloblastic leukemia: a retrospective survey from the acute leukemia working party of the
Therapy for Older AML Patients


