Optimizing Therapy for Acute Myeloid Leukemia

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Abstract
The 10-year overall survival for younger patients with newly diagnosed acute myeloid leukemia has improved threefold in the past 2 decades. This improvement has occurred in large part because of advances in supportive care and efforts to optimize standard induction and consolidation therapies applied in a stratified approach based on predictors of individual patient risk. Innovations in diagnostic technologies have broadened the understanding of key prognostic factors, including cytogenetic and molecular status, which define the extensive interpatient heterogeneity of this clonal disease. Despite this progress, only approximately 25% of patients who experience a complete remission with cytotoxic chemotherapy (50%–70% of patients with newly diagnosed disease) remain disease-free. Efforts to develop novel agents are actively ongoing, particularly for older patients (age ≥ 60), and targeted therapies, for specific subsets of patients are being based on a better understanding of the biology of the disease. (JNCCN 2008;6:1003–1016)

Key Words
Leukemia, myeloid, treatment, cytogenetics, induction, consolidation, transplant

A projected 44,270 new cases of leukemia will be reported in 2008, of which 13,290 are presentations of acute myeloid leukemia (AML). In 2008, more than 20,000 deaths are projected, with 1800 caused by AML. This reflects an 11.5% absolute increase in 10-year survival of patients with newly diagnosed AML relative to 2 decades ago (5.6% in 1980–1984 and 17.1% in 2000–2004). The improvement in survival is the result of the optimization of induction and consolidation dosing regimens; supportive care, including use of antibiotics, antifungals, and hematopoietic growth factors; and efforts to define the role of stem cell transplantation. Stratifying therapy based on age, cytogenetic, molecular, and clinical phenotypes has further improved survival while reducing treatment-related morbidity and mortality, and therefore is integral to treatment approaches. Unfortunately, fewer than 25% of patients, excluding those with acute promyelocytic leukemia, are considered long-term survivors 25 years after diagnosis. The unsatisfactory 12.1-month median survival of 2985 consecutive patients treated on ECOG protocols since 1973 has catalyzed efforts to identify new therapies, including molecularly targeted agents that may significantly influence future outcomes. The hope is that this work will lead to a reexamination of the traditional concepts of induction and consolidation chemotherapy.

Age is the most predictive patient-dependent risk factor for survival. Among patients between ages 15 and 34 years with newly diagnosed AML, 10-year survival improved dramatically during the past 2 decades, from 13.5% to 47.9%, whereas it has only minimally improved for older patients: 0.1% in 1980 through 1984 and 1.0% in 2000 through 2004 (Figure 1). In a retrospective review of 5 SWOG trials, 82% of patients older than 75 years with a performance status of 3 died within 30 days of induction chemotherapy.

In addition to having limiting comorbidities, older patients (age ≥ 60) seem to have a phenotype that is more aggressive and resistant to therapy. For example, 33% of patients younger than 56 years with AML have multidrug resistance (MDR), compared with 57% of those older than 75 years. Favorable and unfavorable cytogenetic status has been reported in 16% and 33% of younger patients, respectively, compared with 4% and 50% of patients older
than 75 years, respectively. Therapy-related AML is 3- to 7-fold more common in older patients with AML and also confers a poor prognosis. Current clinical trials are finally addressing new treatment approaches to improve the long-term survival of older patients with AML.

The heterogeneity of AML is influenced by the diverse array of genetic mutations that may be acquired by the leukemic cells. Approximately 88% of new diagnoses are associated with either cytogenic or molecular mutations. A subset of the remaining 12% of cases with normal karyotype and no molecular mutations express an altered copy number of genespecific mRNA. Cytogenic and molecular abnormalities represent the most predictive, disease-specific risk factor for prognosis. Gene expression profiling using microarray technology has uncovered unique and predictive mRNA and, more recently, microRNA signatures.

Data from multiple trials have established 3 strata of risk according to cytogenetic status (Table 1). Good-risk includes favorable-cytogenic core-binding transcription factor (CBF) mutations with further molecular substratification by c-KIT status and the subset of patients with normal cytogenetics with an NPM1 mutation in the absence of other mutations. Poor-risk includes loss of chromosome 7, inv(3) or t(3;3), complex cytogenetics, and the subset of normal cytogenetic patients with FLT3-internal tandem duplication (ITD). Intermediate-risk is a heterogeneous group with 5-year overall survival (OS) ranging from 13% to 41% and nearly 200 various mutations, including t(11;19)(q23;p13.1), t(6;11)(q27;q23), and t(6;9)(p23;q34) according to Medical Research Council (MRC) data. Although deletions 7q, 9q, 11q, 20q, and t(9;11)(p22;q23) were categorized as adverse risk by SWOG, they have otherwise been considered intermediate risk. Loss of chromosome Y and normal cytogenetics or diploid karyotype are generally accepted as intermediate risk.

Because 45% of de novo AML has a normal karyotype, efforts to identify molecular abnormalities to risk stratify this largest cytogenetic group have been pursued. Only 23.6% of normal cytogenetic AML is truly wild-type based on molecular testing identifying mutations in genes, including CEBPA and NPM1, which carry favorable prognosis (recently confirmed by Schlenk et al.), or MLL, FLT3, BAALC, EVI-1, BCL-2, WT-1, and MN-1 that are associated with unfavorable prognosis (Table 2). Finally, although of unclear influence on clinical outcome, mutations in signaling pathways (particularly in RAS), which occur in 10% to 18% of de novo AML are likely involved in leukemogenesis and will be a target of future therapies.

Treatment

Approach to treatment of acute leukemia has not changed since the institution of combination chemotherapy in 2 treatment phases: induction followed by postremission consolidation. Time to clearance of leukemic blasts with induction therapy influences prognosis. Three risk groups are defined by number of days since initiation of induction therapy required to observe clearance of peripheral blood blasts (≤ day 3, 12.5% relapse risk; day 4 or 5, 47% relapse risk; ≥ day 6, 78% relapse risk). Because of a nearly universal relapse risk within 6 months with induction chemotherapy alone, consolidation therapy is required. Trials have also examined the use of maintenance chemotherapy after consolidation, although its role is not clearly defined. Finally, studies are
ongoing to determine the proper time to consider stem cell transplantation and incorporation of novel therapies.

### Induction

Combination of cytarabine, a cell cycle–specific chemotherapeutic agent, given through continuous infusion for 7 days, and an anthracycline antibiotic (daunorubicin or idarubicin) for 3 days has long been the standard for induction therapy outside of clinical trials. Efforts to improve this regimen, although without success, have included incorporation of high-dose cytarabine, double induction therapy, and addition of other agents, such as etoposide, chlorodeoxyadenosine, and fludarabine. 18–20 The results of 3 trials have shown idarubicin to be superior to daunorubicin. 21–23 Berman et al. 21 showed a superior complete response (CR) rate and median survival of 80% and 19.5 months associated with

### Table 1 Influence of Cytogenetics on Prognosis in Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>Survival (5-y OS [%] or Median Survival [mo])</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC - AML 10</td>
<td>Patients (n) 1612 Age (y)  &lt; 55 Favorable 65% Intermediate 41% Unfavorable 14%</td>
</tr>
<tr>
<td>MRC - AML 11</td>
<td>1065 44–91 34% 13% 2%</td>
</tr>
<tr>
<td>CALGB 8461</td>
<td>1213 15–86 55% 24% 5%</td>
</tr>
<tr>
<td>SWOG S9034 &amp; ECOG E3489</td>
<td>609 56–65 &gt;144 mo 26 mo 11 mo</td>
</tr>
<tr>
<td>SWOG S9034 S9500, S9031, S9333, S0112</td>
<td>968 &gt;75 12 mo 8 mo 4 mo</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; MRC, Medical Research Council; OS, overall survival.

### Table 2 Cytogenetic and Molecular Classification

<table>
<thead>
<tr>
<th>Poor-Risk</th>
<th>Intermediate-Risk</th>
<th>Good-Risk</th>
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<tbody>
<tr>
<td>complex*,† inv(3)(q21q26)/del(3)(q21p13), del(9q)</td>
<td>loss of Y* del(11q), del(11q), del(12q)</td>
<td>inv(16)(p13q22)* or t(8;21)(p13q22)*</td>
</tr>
<tr>
<td>del(7q), loss of 7q</td>
<td>del(9q), del(11q), del(12q)</td>
<td>t(15;17)(q22q12-21)*</td>
</tr>
<tr>
<td>t(6;9)(p23q34), t(6;11)(q27q23) t(11;19)(q23p13.1), t(9;22)</td>
<td>+8, +11, +13, +21, or +22</td>
<td></td>
</tr>
<tr>
<td>del(5q), loss of 5, inv(3) abn11q23 excluding t(9;11)</td>
<td>t(9;11)(p22q23)</td>
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Molecular Stratification of NC‡

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<th>Molecular Stratification of CBF§</th>
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<tbody>
<tr>
<td>Favorable Molecular</td>
</tr>
<tr>
<td>Unfavorable Molecular</td>
</tr>
<tr>
<td>FLT3-ITD*§</td>
</tr>
<tr>
<td>MLL-PTD*</td>
</tr>
<tr>
<td>BAAALC expression*</td>
</tr>
<tr>
<td>ERG expression</td>
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<tr>
<td>EVI-1 expression</td>
</tr>
</tbody>
</table>

Multiple studies support prognostic significance.

1Definition of complex cytogenetics among younger population defined as ≥3 cytogenetic abnormalities, excluding inv(16), t(16;16), t(8;21), t(15;17), or t(9;11), and among older patients with AML defined as ≥5 cytogenetic abnormalities.

‡Normal-cytogenetic AML is stratified by molecular status.

§Core-binding factor (CBF) AML, including t(8;21) and inv(16) or t(16;16), is stratified by molecular status.

§FLT3-ITD among normal cytogenetic AML is considered poor risk, NPM1 mutation among normal cytogenetic AML is considered good risk, and c-KIT mutation among CBF-AML is considered intermediate risk by NCCN clinical practice guidelines in oncology: Acute Myeloid Leukemia. 14
idarubicin compared with 58% and 13.5 months, respectively, with daunorubicin, both in combination with cytarabine. In the series reported by Wiernik et al., idarubicin improved response rates and survival among patients aged 18 to 50 years, with a CR rate of 88% and median survival of 12.9 months, respectively, compared with 70% and 8.7 months, respectively, among patients of all ages. Vogler et al. reported superior CR rates and median survival in their idarubicin arm: 71% versus 58% and 433 versus 328 days, respectively.

In 1998, the AML Collaborative Group meta-analysis of 5 trials (325 patients randomized to idarubicin and 283 to daunorubicin) observed a trend toward increased disease-free survival (DFS), with a 15% relapse risk reduction and a statistically significant 14% risk reduction for death favoring idarubicin. A criticism of these studies, however, is their nonequivalent anthracycline dosing, with lower myelosuppressive doses of daunorubicin relative to idarubicin. This criticism was addressed in the Acute Leukemia French Association (ALFA) 9801 trial that reported a series of 468 patients randomized to cytarabine with daunorubicin 80 mg/m²/d for 3 days or idarubicin 12 mg/m²/d for 3 or 4 days. Overall response rates (ORRs) and CR rates after the first course of induction were superior in the idarubicin arm, at 83% ORR and 62% CR for 3 days of idarubicin and 78% ORR and 57% CR for 4 days of idarubicin, versus 71% ORR and 45% CR with daunorubicin. Despite the findings, idarubicin shows no clear benefit compared with other anthracyclines.

Mitoxantrone, an anthraquinone, has been compared with standard anthracyclines in older patients with AML with equivalent response and survival. When comparing mitoxantrone with idarubicin or daunorubicin, each in combination with standard-dose cytarabine, Rowe et al. found that neither CR rates (observed in 46%, 43%, and 40%, respectively) nor median OS (7.2, 7.5, and 7.7 months, respectively) were statistically different. These results are in contrast to the results of a recent European study randomizing 2157 patients to daunorubicin, mitoxantrone, or idarubicin, with each arm receiving cytarabine and etoposide. CR rates were similar for all 3 arms; however, among patients with no available donor for stem cell transplantation, the idarubicin and mitoxantrone arms showed superior DFS compared with daunorubicin.

Finally, 2 studies examined the role of adding etoposide or fludarabine to the induction regimen. The Australian Leukemia Study (ALSG) added etoposide to daunorubicin and cytarabine, and found no improvement in remission rates. In subset analysis, OS was prolonged in patients younger than 55 years with the addition of etoposide (17 vs. 9 months). The addition of fludarabine or etoposide to idarubicin and cytarabine did not improve outcome, although it resulted in greater efficacy in overcoming P-glycoprotein–mediated MDR.

Although cytarabine has been a backbone of induction therapy, a series of trials have addressed its optimal dosing, comparing standard- versus high-dose treatment (Table 3). These 3 trials showed no difference in CR rate, and superior DFS (excluding the subset of patients in SWOG aged 50–64 years), but OS data was heterogeneous. Furthermore, a meta-analysis by Kern and Estey reported no difference in median OS and a 6-fold weighted-mean difference in 4-year OS favoring high-dose cytarabine. Because of the toxicity of high-dose induction chemotherapy, including a nearly 4-fold higher rate of grade 3/4 neurotoxicity, postremission treatment was precluded in a significant subset of patients. High-dose induction chemotherapy use is limited because of the risk for toxicity.

Further dose-intensification in double-induction regimens was tested by the German AML cooperative group (AMLCG), with long-term results recently published. In this large trial, 1770 patients were randomized to double-induction with 2 courses of high-dose cytarabine compared with 1 standard- and 1 high-dose cycle without statistically superior efficacy (53% vs. 70% CR and 19% vs. 42% 3-year OS, respectively).

**Consolidation**

Recognizing that high-dose induction chemotherapy followed by consolidation produced OS rates as high as 52% among young patients, a CALGB trial attempted to show similar efficacy with less toxicity using high-dose consolidation chemotherapy after standard-dose induction. In this trial, 1088 patients received standard induction with daunorubicin and cytarabine followed by randomization to 1 of 3 doses of cytarabine; 100 mg/m²/d for 5 days, 400 mg/m²/d for 5 days, or 3000 mg/m² every 12 hours (6000 mg/m²/d) for 3 days, on days 1, 3, and 5. DFS at 52 months was
superior in the high-dose consolidation arm (hazard ratio, 0.67). However, the 4-year DFS benefit seen in patients aged 60 years and younger (44% vs. 24%) was not observed in those older than 60 years (DFS ≤ 16%), partially because the older patients had a 5% treatment-related mortality and 12% severe neurologic toxicity. Subset analysis showed superior DFS with high-dose cytarabine for patients with good-risk cytogenetics, marginal benefit with intermediate-risk cytogenetics, and no benefit with poor-risk cytogenetics (Fig. 2A–C). Among patients with CBF-AML treated with high-, intermediate-, and standard-dose cytarabine consolidation, 5-year CR was observed in 78%, 57%, and 16%, respectively. The benefit was less marked among patients with normal-karyotype AML, with no benefit seen in those with poor-risk cytogenetics (21%, 13%, and 13% CR, respectively).

Stein et al.14 showed improvement in CR with high-dose cytarabine during induction among favorable-, intermediate-, and poor-risk patients (87%, 79%, and 62% CR, respectively). This issue has been revisited by Neubauer et al.,16 who recently showed that patients with RAS mutations who receive high-dose cytarabine have fewer relapses compared with those with wild-type mutations (45% vs. 68%). The interdependence of these observations has not been explored.

A series of CALGB trials have addressed the role of high-dose cytarabine consolidation in improving outcome in CBF-AML.15–17 Extended cycles of consolidation (3 vs. 1) among patients with t(8;21) were associated with superior outcome, with a 19% relapse rate and 76% OS among patients receiving 3 or more cycles versus 62% and 41%, respectively, among those receiving a single cycle.17 Likewise, among patients with inv(16) or t(16;16), relapse was significantly decreased with extended cycles of consolidation, although no difference in OS was observed.16 In CALGB 9222, sequential multiagent chemotherapy, including one course of high-dose cytarabine followed by etoposide and cyclophosphamide, and a third course of mitoxantrone and diaziquone, showed no difference in median DFS, 1-year survival, or median OS when compared with 3 cycles of high-dose cytarabine.18 A recent retrospective review of 370 patients by Appelbaum et al.19 suggests that the superior prognosis associated with CBF-AML may not be as significant as previously reported.

**Maintenance**

Despite the established role of maintenance therapy in acute lymphoblastic leukemia and acute promyelocytic leukemia, its role in AML is less clear. In 1978, the German AMLCG reported the results of a

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**Table 3 Standard-Dose Versus High-Dose Cytarabine in AML Induction Therapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Age (y)</th>
<th>High-Dose Arm</th>
<th>Standard Arm</th>
<th>Additional Chemotherapy</th>
<th>CR (%)</th>
<th>ED (%)</th>
<th>DFS (m)</th>
<th>OS (%)</th>
<th>4-y OS (%)</th>
<th>SE (%)</th>
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<tbody>
<tr>
<td>ALSG</td>
<td>149</td>
<td>15-60</td>
<td>6000 mg/m² x 4 d</td>
<td>—</td>
<td>DNR + VP-16</td>
<td>106</td>
<td>71</td>
<td>27</td>
<td>18</td>
<td>22* 19* 34*</td>
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<tr>
<td>SWOG</td>
<td>152</td>
<td>15-60</td>
<td>—</td>
<td>100 mg/m² x 7 d</td>
<td>DNR + VP-16</td>
<td>112</td>
<td>74</td>
<td>17</td>
<td>11</td>
<td>12* 17* 25*</td>
<td>0</td>
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<tr>
<td>SWOG</td>
<td>85</td>
<td>15-49</td>
<td>4000 mg/m² x 6 d</td>
<td>—</td>
<td>DNR</td>
<td>47</td>
<td>55</td>
<td>12* 14*</td>
<td>14* 12* 13* 32*</td>
<td>7</td>
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<tr>
<td></td>
<td>293</td>
<td>15-49</td>
<td>—</td>
<td>200 mg/m² x 6 d</td>
<td>DNR</td>
<td>170</td>
<td>58</td>
<td>18* 6*</td>
<td>10* 17* 22*</td>
<td>5* 28*</td>
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<tr>
<td></td>
<td>87</td>
<td>50-64</td>
<td>4000 mg/m² x 6 d</td>
<td>—</td>
<td>DNR</td>
<td>39</td>
<td>45</td>
<td>17* 20*</td>
<td>8</td>
<td>7 13* 14* 24*</td>
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<tr>
<td></td>
<td>200</td>
<td>50-64</td>
<td>200 mg/m² x 6 d</td>
<td>—</td>
<td>DNR</td>
<td>105</td>
<td>53</td>
<td>17* 9*</td>
<td>8</td>
<td>8 11* 1* 6*</td>
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<tr>
<td>AMLCG</td>
<td>365</td>
<td>16-60</td>
<td>6000 mg/m² x 3 d</td>
<td>—</td>
<td>mitoxantrone</td>
<td>259</td>
<td>71</td>
<td>51</td>
<td>14</td>
<td>23 20* 36*</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>16-60</td>
<td>—</td>
<td>200 mg/m² x 7 d</td>
<td>DNR + TG</td>
<td>234</td>
<td>65</td>
<td>65</td>
<td>18</td>
<td>18* 18* 32*</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: ALSG, Australian Leukemia Study Group; AML, acute myeloid leukemia; AMLCG, German Acute Myeloid Leukemia Cooperative Group; CR, complete response; DFS, disease-free survival; DNR, daunorubicin; ED, early death; OS, overall survival; SE, side-effect specifically grade III, IV, or V neurologic toxicity; TG, thioguanine; VP-16, etoposide.

*Statistically significant (P < .05).
In 1981, Rai et al. published the findings of a CALGB study of 358 patients who underwent standard induction chemotherapy followed by maintenance with cytarabine, 100 mg/m², subcutaneously or intravenously twice daily for 5 days along with either thioguanine, cyclophosphamide, lomustine, or daunorubicin given in monthly cycles for 4 to 5 years. Median survival was 35 months with standard induction and subcutaneous cytarabine, the longest reported survival in a prospective AML trial. Subsequent studies, including AMLCG 81, AMLCG 92, ECOG E5483, SWOG 8124, and AML 9 (HOVON), each confirmed improved DFS, although not OS, with maintenance chemotherapy. Japan Leukemia Study Group AML 87 reported superior DFS, although not OS, after 12 versus 4 cycles of cytarabine, daunorubicin, mercaptopurine, and vincristine maintenance.

Although maintenance therapy has proven beneficial in improving DFS, it has not consistently shown improved OS in patients with de novo AML undergoing induction and consolidation chemotherapy. Negative trials include AMLCG 99 (cytarabine maintenance with 1770 subjects), Swiss Group for Clinical Cancer Research (SAKK; combination cytotoxic chemotherapy maintenance), MRC AML 11 (combination cytotoxic chemotherapy maintenance), ALFA 9801 (interleukin [IL]-2 maintenance), CALGB 19808 (IL-2 maintenance), CALGB 8923 (mitoxantrone and cytarabine maintenance), and ECOG 3483 (cytarabine maintenance). CALGB 7921 reported a suggestion of worse OS with 3 years versus 8 months of thioguanine and cytarabine maintenance. One caveat to prior negative trials of maintenance chemotherapy is that only standard cytotoxic chemotherapy or IL-2 was used. Trials of molecular targeted therapies, antibody therapeutics, hypomethylating agents, and tyrosine kinase inhibitors as maintenance strategies are ongoing.

**Stem Cell Transplantation**

Eleven major trials, involving 9109 patients, have examined the role of stem cell transplantation as postremission therapy for AML (Table 4). The results suggest no convincing role for autologous stem cell transplant as postremission therapy. However, for younger patients with intermediate- and poor-risk cytogenetics with a suitably matched donor, allogeneic

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**Figure 2** Complete remission (CR) duration within specific groups by cytarabine dose intensification. (A) Core-binding transcription factor (CBF)-AML; (B) normal cytogenetic AML; (C) other (non-CBF or normal cytogenetic) AML. Reproduced from Bloomfield CD, Lawrence D, Byrd JC, et al. Frequency of prolonged remission duration after high-dose cytarabine intensification in acute myeloid leukemia varies by cytogenetic subtype. Cancer Res 1998;58:4173–4179; with permission.
transplantation seems to confer superior DFS compared with traditional chemotherapy.

This finding contrasts with the retrospective review of 999 patients by Ferrant et al. that observed similar benefit with allogeneic and autologous transplantation for patients with unfavorable karyotype, and a benefit to allogeneic transplantation only in patients with favorable- or standard-risk cytogenetics. Nonetheless, the recent findings are supported by the HOVON/SAKK analysis of 3 prior trials using a “donor versus no donor” approach assessing 2287 patients in first CR, and a meta-analysis of 3103 patients by Ferrant et al. Among patients with normal-karyotype AML, only those experiencing first remission without the molecular phenotype fitted in 4 prior AMLCG trials (AML 2/95, AML 1/99, AML HD93, and AML HD98A). Among patients with normal-karyotype AML, only those experiencing first remission without the molecular phenotype NPM1+/CEBPA-/FLT3+ or with NPM1-/CEBPA-/FLT3-ITD+ benefit from allogeneic transplantation (Fig. 3A, B).

In a similar approach, Power et al. evaluated FLT3-ITD status among 267 patients who underwent transplantation and showed no difference in survival among FLT3-ITD+ and wild-type FLT3 AML, arguing that allogeneic transplantation improved prognosis of AML patients with FLT3 mutations, overcoming the typically negative prognosis of this subset of patients. Finally, current transplant strategies are extending the upper age of transplantation showing OS of 51% and 45% at 3 and 4 years, respectively, in older patients with AML experiencing first or second complete remission.

### AML in Older Patients

Treatment of AML in older patients remains unsatisfactory, with DFS less than 15% at 3 years.
and minimal improvement in prognosis (Fig. 1). Appelbaum et al. reviewed 5 prior SWOG studies and reaffirmed the association of increasing age with less favorable cytogenetics and poor performance status, factors that contribute to poor outcomes (Fig. 4A–C). Prior trials attempting to improve prognosis in older patients with AML using strategies such as incorporating growth factor support (ECOG E3993), intensifying cytarabine, and modifying the chemotherapy dosing schedule showed no improved survival. Minor improvement in CR rates has been achieved through incorporating alternative cytotoxic chemotherapeutics, including thioguanine in MRC AML 11, mitoxantrone and etoposide in SWOG 9333, and modified idarubicin and cytarabine in the M. D. Anderson case series reported by Estey et al. Each of these advances is limited by short durability of response. In older patients with AML, maintenance chemotherapy trials, including combination of thioguanine, cytarabine, and daunorubicin, failed to improve OS, although median DFS increased from 12 to 19 months. Minority improvement in CR rates has been achieved through incorporating alternative cytotoxic chemotherapeutics, including thioguanine in MRC AML 11, mitoxantrone and etoposide in SWOG 9333, and modified idarubicin and cytarabine in the M. D. Anderson case series reported by Estey et al. Each of these advances is limited by short durability of response. In older patients with AML, maintenance chemotherapy trials, including combination of thioguanine, cytarabine, and daunorubicin, failed to improve OS, although median DFS increased from 12 to 19 months. At 4 to 5 years, only 13% of the 297 patients remained in CR. ALFA 9803, randomized patients aged 65 years and older to idarubicin or daunorubicin with either a single cycle or 6 cycles of maintenance chemotherapy. No difference between anthracyclines was observed, and despite improved DFS with maintenance, no OS benefit was shown. Results of MRC AML 14 reported in 2005 showed a 5-year DFS of only 13%, which was identical to that reported a decade earlier.

New agents for older patients with AML have the most promise for improving OS in this poor-risk subset. Agents recently approved or currently in trials include gemtuzumab ozogamycin, clofarabine, tipifarnib, cloretazine, MDR inhibitors, bcl-2 antisense, and hypomethylating agents.

**Novel Agents**

Newer therapies include gemtuzumab ozogamycin, a calicheamicin-conjugated monoclonal antibody directed toward CD33 approved for patients aged 60 years and older experiencing their first recurrence after a CR of at least 3 months. Gemtuzumab monotherapy has also been assessed in previously untreated, older patients with AML, including 16 with a 25% CR rate. Dose-limiting hepatotoxicity and bone marrow suppression was observed, along with neutropenic fever in 10 of 16 patients.

Pirrotta et al. piloted combination induction incorporating gemtuzumab in 12 patients, using a regimen that also included fludarabine, cytarabine, and idarubicin, followed by 2 courses of consolidation with gemtuzumab. CRs were observed in 75% of patients with no treatment-related mortality. Similarly, incorporating gemtuzumab into standard induction with daunorubicin and cytarabine produced a 38% CR and
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12.5% partial response rate among a limited cohort of patients.

In a report of findings from MRC AML 15, Burnett et al. focused on the role of gemtuzumab in either induction or consolidation in younger patients with previously untreated AML, with induction including randomization to daunorubicin and cytarabine; cytarabine, daunorubicin, and etoposide; or cytarabine, idarubicin, fludarabine, and granulocyte colony-stimulating factor. Consolidation involved etoposide and cytarabine or high-dose cytarabine. Among 1115 randomized patients, 83% expressed CD33. Although no difference in OS was seen at 15 months, the rate of relapse decreased from 52% to 37% at 3 years. The benefit to treatment seemed limited to patients with favorable- and intermediate-risk cytogenetics. As this trial matures, patients continue to be followed-up for OS. A small subset of approximately 140 patients in this trial were at least 60 years old, in whom a striking CR rate of 82% was observed. At least 7 trials are currently examining the role of gemtuzumab as maintenance therapy, consolidation therapy before autologous stem cell transplantation, part of induction, and monotherapy in previously untreated older patients.

Clofarabine is an adenosine nucleoside analog approved for pediatric acute lymphoblastic leukemia. A phase II adult trial reported a 60% ORR and 52% CR rate with clofarabine in combination with cytarabine as induction therapy in newly diagnosed AML, with an acceptable 7% treatment-related mortality. Among patients previously untreated and unfit for standard induction, clofarabine monotherapy has reasonable initial efficacy, with a 48% CR. Clofarabine, a nucleoside analog, with 13% ORR in phase I trials, has been shown to produce 40% to 55% CR in combination with cytarabine or idarubicin in older patients with newly diagnosed AML with unfavorable karyotype.

Molecular targeted therapies include several inhibitors of FLT3 kinase. FLT3 is an FMS-like tyrosine kinase that influences myeloid differentiation and has 2 common mutational positions. FLT3-ITD within the juxtamembrane domain occurs in 20% to 30% of patients with AML, whereas mutations in the tyrosine kinase domain occur in 5% to 10%. FLT3-ITD confers a negative prognosis, with worse OS and higher relapse rate, that is influenced by loss of underlying wild-type FLT3 and possibly by size and copy number of ITDs in the mutant allele. An oral FLT3 inhibitor CEP701 (lestaurtinib) is being evaluated in the salvage setting with an improved response rate seen in preliminary results. FLT3 inhibitors are also being explored.

Figure 4 Overall survival by age and cytogenetic risk. (A) Unfavorable risk cytogenetics: median survival (MS) 11 months (< 56 years), MS 5 months (56–65 years), MS 4 months (66–75 and > 75 years). (B) Intermediate risk cytogenetics: MS 26 months (< 56 years), MS 12 months (56–65 years), MS 8 months (66–75 years), MS 7 months (> 75 years). (C) Favorable risk cytogenetics: MS not reached (< 56 and 56–65 years), MS 12 months (66–75 and > 75 years).

In older patients with AML who are otherwise not candidates for standard induction regimens.\textsuperscript{71}

In a phase II trial, oral CEP701 was well tolerated for 8 weeks, with transfusion independence in 60\% of patients with FLT3 mutations and 23\% in wild-type FLT3. PKC412, a second targeted FLT3 inhibitor, has shown favorable CR rates (92\% for mutated and 69\% for wild-type FLT3) in combination with standard induction chemotherapy in young patients.\textsuperscript{39} Mutations in exon 17 of KIT, which encodes the activation loop, are associated with reduced OS from 1836 to 304 days in patients with CBF-AML. Inhibition of other kinases, including c-KIT, may show efficacy in a subset of CBF-AML, with one trial involving dasatinib, a c-KIT inhibitor, currently ongoing.

Tipifarnib (R115777), a farnesyl transferase inhibitor, was used in combination with standard induction, consolidation, and maintenance chemotherapy without improvement in CR rates. In older patients with untreated AML, phase II studies showed a 14\% CR rate and 23\% ORR.\textsuperscript{39} Nonhematologic serious adverse effects were observed in 47\% of patients, potentially limiting its use in the older population. When used in combination with etoposide as induction for older patients with AML, CRs occurred in 25\%.\textsuperscript{80}

Because of the increased incidence of MDR efflux mechanisms in older AML patients, multiple new agents targeting this mechanism of drug resistance are currently in trials. This strategy was validated by the use of cyclosporine A (CsA) to inhibit MDR in a randomized phase III SWOG trial for relapsed or refractory AML.\textsuperscript{81} DFS and OS at 2 years both improved significantly with CsA (34\% vs. 9\%, and 22\% vs. 12\%, respectively). This finding was further supported by the SWOG study of high-risk patients, in which CR rate was independent of P-glycoprotein status, and serum daunorubicin levels were increased in the group receiving the MDR modulator.\textsuperscript{82} However, in the ECOG 2995 trial of patients with poor-risk AML and high-risk MDS, no benefit in response rate was seen in those receiving PSC-833, an MDR modulator.\textsuperscript{83}

In CALGB 9720, PSC-833 combined with daunorubicin, etoposide, and cytarabine led to excessive mortality compared with the PSC-833 arm (44\% vs. 20\%, respectively), requiring early trial termination. Zosuquidar, a third-generation MDR modulator, developed as a more specific P-glycoprotein inhibitor, was used along with standard chemotherapy in ECOG 3999. No difference was observed in overall or median survival with or without zosuquidar (7.7 vs. 9.4 months, respectively).\textsuperscript{84} In a separate trial, 62 patients specifically with P-glycoprotein+ AML received zosuquidar and achieved CR or near CR in 48\%, with ORR in 57\%.\textsuperscript{85}

In 3 CALGB trials, 5-azacitidine, a hypomethylating agent, showed reasonable efficacy and a tolerable toxicity profile.\textsuperscript{86} CRs were observed in 10\% to 17\% of patients with myelodysplasia or AML, with hematologic improvements in an additional 23\% to 36\%. Median survival of patients with AML was 19 months, compared with 13 months in patients receiving placebo. Decitabine or 5-aza-2-deoxycytidine, a similar pyrimidine analog, induced overall responses in 32\% of 50 patients with relapsed or refractory AML.\textsuperscript{78} The combination of azacitidine with a histone deacetylase inhibitor, MGCD0103, may have a role through modulation of the epigenetic status of AML. A pilot study showed a 30\% ORR, with 4 CRs. A second combination study with azacitidine incorporated gemtuzumab in older patients with AML or high-risk myelodysplasia, showing a 76\% CR rate and a median response duration of 7 months.\textsuperscript{80}

Efforts to target leukemic stem cells seem promising. Although early trials of oblimersen, a BCL-2 inhibitor, were positive, the phase III CALGB 10201 trial failed to show a benefit, resulting in early study closure. Because of expression of IL3-Rα (CD123) by leukemic stem cells, phase I trials of IL-3 in combination with diphtheria toxin are ongoing. In a phase I trial of diphtheria toxin–IL-3 fusion protein among 40 patients, antibody development occurred in most by day 40, but only 1 CR and 1 PR were observed.\textsuperscript{89}

Parthenolide is a sesquiterpene lactone that selectively induces leukemic stem cell apoptosis in vitro. An orally bioavailable parthenolide has been reported to show promising preclinical activity, but must be studied in clinical trials to determine its safety and efficacy. Multiple other potential leukemia stem cell targets are being actively explored, including CD44, CXCR4, CD123, and NF-kappaB.

**Conclusions**

The next decade of optimizing AML therapy will incorporate new cytotoxic and novel targeted therapies into the standard approach for AML treatment, because today they remain limited to clinical trials. Stratification of patient risk and selection of therapy...
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has benefited greatly by technologic advances in cytogenetic and molecular assessment. Technical innovations within the next decade may allow continuous monitoring of minimal residual disease. Current molecular and immunophenotyping methodologies can detect evidence of leukemic clones in 80% of patients at levels not possible using standard morphology, metaphase cytogenetics, or interphase fluorescence in-situ hybridization. Preliminary findings from the MRC AML 15 trial show that real-time quantitative PCR allows detection of minimal residual disease in CBF-AML and predicts early relapse. Assuming that minimal phenotype shift of the leukemic clone occurs with treatment and over extended periods and that early institution of therapy can improve OS, the ability to monitor minimal residual disease offers the promise of novel pre-emptive treatment strategies. Finally, future optimization of treatment approaches to AML will include efforts to expedite drug approval and properly define study end points incorporating CR without platelet recovery, markers of minimal residual disease, measures of “bridge to transplant,” and patient quality-of-life metrics.

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