Introduction

Approximately 50%-75% of adults with acute myeloid leukemia (AML) achieve complete remission (CR) with an anthracycline and cytarabine. However, long-term disease-free survival (DFS) occurs in only 20%-30% of patients who achieve CR. The majority of patients with AML still die of their disease.

The Eastern Cooperative Oncology Group (ECOG) has recently reviewed the outcome for more than 1,400 patients with previously untreated AML entered on five successive clinical trials. Each trial included daunorubicin and cytarabine for induction. Successive trials in this analysis included postremission therapy with increasingly more intensive consolidation. Among 1,414 patients, 62% achieved CR, but 76% have relapsed or died. The overall survival (OS) rate for all patients at 5 years is only 15%. Patients aged 55 years or older fared particularly poorly. The 5-year OS rate was 9%-33% for patients less than 55 years of age and 6%-15% for patients aged 55 years and older. Among patients less than age 55 years, both the DFS and OS increased with more intensive postremission strategies.

The outcome for adults with AML depends on several factors: the age of the patient, the intensity of postremission therapy, and the biologic characteristics of the disease, including karyotype and expression of the multidrug resistant (MDR) phenotype. The French-American-British (FAB) classification has been widely adopted and has promoted uniformity of diagnosis of morphologic subtypes of AML. It remains useful in identifying certain biologic subtypes but does not, by itself, account for all subtypes. The diagnosis and prognosis is based not only on the FAB classification, but also on cytogenetics, immunophenotyping, and molecular genetics. Such advances have led to a new proposed World Health Organization classification that attempts to correlate morphology, cytochemistry, immunophenotype, karyotype, and molecular genetics with clinical features. Several host-related and disease-related factors have prognostic importance including age older than 60 years, the presence of an antecedent myelodysplastic syndrome, elevated white blood cell count, karyotype, and expression of the MDR phenotype. The initial karyotype has emerged as one of the most important independent prognostic factors and can distinguish three groups with prognostic value (Fig 1): (1) favorable: t(15;17), t(8;21), inv(16), (2) intermediate: normal karyotype, trisomy 8, 11q23, del(7q), del(9q), trisomy 22, other numerical abnormalities, or (3) adverse: complex karyotype, -7, -5, del(5q), abn(3q). However, such classifications do not completely account for karyotypes with multiple abnormalities, each with its independent prognostic value, the importance of molecular detection of specific abnormalities and variants, or the potential influence of associated antigen expression. Advances in outcome have occurred primarily in supportive
Induction Chemotherapy

During the past 30 years, a series of studies has identified an induction regimen that is considered standard. Approximately 30%–40% of patients achieve CR with either cytarabine or daunorubicin given as a single agent.\(^{26-28}\) CR was achieved in more than 50% of patients when these agents were combined. The Cancer and Leukemia Group B established that a regimen of 3 days of daunorubicin and 7 days of cytarabine was better than 2 days and 5 days, respectively, and that 10 days of cytarabine was not better than 7 days.\(^{1,29}\) Daunorubicin at a dose of 30 mg/m\(^2\) proved to be inferior to 45 mg/m\(^2\) in patients less than 60 years of age and less toxic than 30 mg/m\(^2\) of doxorubicin.\(^{2}\) Finally, 100 mg/m\(^2\) of cytarabine was found to be equally effective as 200 mg/m\(^2\).\(^{30}\) Therefore, the most widely used combination for induction chemotherapy today is daunorubicin at 45 mg/m\(^2\) per day intravenously (IV) for 3 days, cytarabine at 100 mg/m\(^2\) per day IV for 3 days, and cytarabine 100 mg/m\(^2\) by continuous IV infusion for 7 days.

A number of studies have been conducted recently to improve the CR rate. Some trials have tested new agents such as etoposide or high-dose cytarabine (HiDAC).\(^{31}\)

### Anthracyclines in Induction Therapy

The anthracyclines include daunorubicin, doxorubicin, aclacinomycins, the synthetic anthracyclines, mitoxantrone, and the synthetic agent 4-demethoxydaunorubicin (idarubicin). Idarubicin may be better as an induction agent.

### Table 1. Randomized Trials of Idarubicin (I) vs Daunorubicin (D)

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Median Age (years)</th>
<th>CR Rate (%)</th>
<th>CR Cycle 1 (%)</th>
<th>Resistant Leukemia (%)</th>
<th>Median OS (months)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman</td>
<td>I 60 D 60</td>
<td>I 36 D 41</td>
<td>I 80 D 58 P&lt;.005</td>
<td>I 75 D 49</td>
<td>I 8 D 21</td>
<td>I 20 D 14</td>
<td>.025</td>
</tr>
<tr>
<td>Wierink</td>
<td>I 97 D 111</td>
<td>I 56 D 55</td>
<td>I 70 D 59 P=.08</td>
<td>I 55 D 38</td>
<td>I 6 D 22</td>
<td>I 13 D 9</td>
<td>.038</td>
</tr>
<tr>
<td>Vogler</td>
<td>I 105 D 113</td>
<td>I 60 D 61</td>
<td>I 71 D 58 P=.03</td>
<td>I 77 D 78</td>
<td>I 10 D 18</td>
<td>I 11 D 9</td>
<td>.0913</td>
</tr>
<tr>
<td>Mandelli</td>
<td>I 124 D 125</td>
<td>I 63 D 62</td>
<td>I 40 D 39 NA</td>
<td>I 74 D 51</td>
<td>I 14 D 31</td>
<td>I 3 D 6</td>
<td>.23</td>
</tr>
</tbody>
</table>

CR = complete remission
OS = overall survival
NA = not available

because of its higher lipid solubility, increased cellular uptake, induction of more DNA single-strand breaks, conversion to an alcoholic derivative (13-hydroxyidarubicin, an active metabolite with a prolonged plasma half-life), greater toxicity of AML blast cells, and less dependency on P-glycoprotein efflux.32-35

Four prospective randomized trials comparing idarubicin to daunorubicin suggest that idarubicin may have benefits, particularly in young adults (Table 1).36-39 In three of the studies, idarubicin was associated with a significantly higher CR rate, particularly in younger patients, was more effective in eradicating leukemia after one course, and was associated with a lower incidence of resistant leukemia. The study by Mandelli and colleagues39 for the Gruppo Italiano Malattie Ematologiche Maligne dell’Adul to (GIMEMA) was the only trial that did not show a higher CR rate with idarubicin. This trial included patients with preexisting myelodysplasia who were excluded by Berman and colleagues.36 Although patients with an antecedent myelodysplastic syndrome were eligible in the studies by Wiernik et al37 and Vogler et al,38 few such patients were included. The GIMEMA study39 included only patients older than 55 years of age, whereas the other two studies did not restrict the upper age limit. The CR rate with idarubicin was not unfavorably influenced by hyperleukocytosis in the studies by Berman and colleagues36 and Wiernik et al,37 but it was with daunorubicin.

Higher CR rates have been achieved with idarubicin compared to daunorubicin in younger patients. Idarubicin may be beneficial in patients presenting with hyperleukocytosis. In these prospective studies, idarubicin at either 12 or 13 mg/m² was compared to daunorubicin at a dose of 45 mg/m². Therefore, it may be possible that a higher dose of daunorubicin may confer the same apparent benefits observed with idarubicin. A prospective randomized trial has not been conducted that compares daunorubicin at a dose of 45 mg/m² to either 60 mg/m² or 70 mg/m². Furthermore, it is not clear that OS with idarubicin is superior to that achieved with daunorubicin since two studies showed an advantage and two did not. A meta-analysis by the AML Collaborative Group40 reported similar early induction failure rates (20% for idarubicin vs 18% for daunorubicin, P=0.4), but fewer late (after day 40) induction failures with idarubicin (62% vs 53%, P=0.002). Among patients achieving CR, fewer patients assigned to idarubicin relapsed (P=0.008) but somewhat more died in CR, resulting in a nonsignificant benefit in DFS (P=0.07). OS was better with idarubicin compared with daunorubicin, with 13% vs 9%, respectively, alive at 5 years (P=0.03) (Table 2). Therefore, there is level 1, grade

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Daunorubicin (n = 521)</th>
<th>Idarubicin (n = 532)</th>
<th>NNT or NNH (95% CI)</th>
<th>ARR (95% CI)</th>
<th>RRR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Complete Remission</td>
<td>53%</td>
<td>62%</td>
<td>11</td>
<td>9%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 to 3</td>
<td>3% to 15%</td>
<td>5% to 29%</td>
<td></td>
</tr>
<tr>
<td>Early Death</td>
<td>18%</td>
<td>20%</td>
<td>50</td>
<td>2%</td>
<td>-3% to 7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 to -37*</td>
<td>-3%* to 7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late Failure</td>
<td>29%</td>
<td>17%</td>
<td>8</td>
<td>12%**</td>
<td>7% to 17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 to 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of Evidence/Grade</td>
<td>1, meta-analysis/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Minus sign (-) denotes that daunorubicin may be more toxic (ie, NNH ranges from NNHIDA15 to = to NNHIDA37.

** Daunorubicin has more late failures.

NNT = number needed to treat to avoid 1 adverse outcome
NNH = number needed to treat to harm 1 individual
CI = confidence interval
RRR = relative risk reduction
ARR = absolute risk reduction

Evidence (Table 3) that, in younger patients, idarubicin is superior to daunorubicin.

Mitoxantrone is associated with a relatively steep dose-response rate in clonogenic assays of leukemia cells and has a favorable extramedullary toxicity profile. Mitoxantrone and aclarubicin, a class III anthracycline whose uptake and outward transport is largely unaffected in MDR cell lines, may also offer advantages. In the studies reported to date, mitoxantrone appears at least as effective and aclarubicin more effective than daunorubicin in younger patients with respect to CR rate but not OS, and both may be associated with less-resistant leukemia.

In a comparative trial, cytarabine and 6-thioguanine were combined with amsacrine (a DNA intercalator distinct from anthracyclines) or 50 mg/m² of daunorubicin. Amsacrine given with cytarabine and 6-thioguanine was associated with a higher CR rate compared with daunorubicin (70% vs 54%, P=0.03), more frequent achievement of CR with only one cycle (48% vs 28%, P=0.03), and improved OS (P=0.01).

Several other studies have addressed the dose and choice of anthracyclines specifically in older adults. Buchner and colleagues compared daunorubicin at 30 mg/m² and at 60 mg/m² during induction in patients older than 60 years of age, followed by consolidation and monthly maintenance for 3 years. The CR rate was higher among patients receiving the larger dose (52% vs 45%, P=0.026), and it was higher after one cycle (38% vs 20%, P=0.001). Survival was significantly improved only among patients older than age 65 (14% vs 5%, P=0.002). A small trial by Feldman and colleagues compared mitoxantrone at 80 mg/m² given once (high-dose) with 36 mg/m² given over 3 days (standard-dose). CR was achieved in 57% of patients on the high-dose arm compared with 43% on the standard-dose arm. However, the median time to relapse was 6 months, and there was neither a statistically significant difference between the two groups nor a difference in toxicity.

ECOG has completed a prospective randomized trial in older adults of daunorubicin vs idarubicin vs mitoxantrone as the anthracycline given with cytarabine. A total of 350 evaluable patients were accrued. A preliminary analysis shows that the CR rates achieved with the three different anthracyclines did not differ. There was a trend toward a decreased induction mortality rate on the mitoxantrone arm. In the collaborative trial of the European Organization for Research and Treatment of Cancer (EORTC) and the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON), patients 60 years of age and older were randomized to receive either 30 mg/m² of daunorubicin for 3 days or 8 mg/m² of mitoxantrone for 3 days plus cytarabine 100 mg/m² by continuous infusion for 7 days. There was a modestly higher CR rate with mitoxantrone compared with daunorubicin (46.6% vs 38.0%, P=0.067) that was likely related to a reduced probability of resistant leukemia (47% vs 32%, P=0.001) since the induction mortality was somewhat higher with mitox-

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
<th>Grade of Recommendation</th>
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<tbody>
<tr>
<td>1</td>
<td>Meta-analyses or individual randomized trials in which the lower limit of the confidence interval for the treatment effect exceeds the minimal clinically important benefit</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>Meta-analyses or individual randomized trials in which the lower limit of the confidence interval for the treatment effect exceeds the minimal clinically important benefit</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>Nonrandomized concurrent cohort studies</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>Nonrandomized historic cohort studies</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>Case series</td>
<td>C</td>
</tr>
</tbody>
</table>

antrone (21% vs 15%). However, among patients who achieved CR, there was no difference in DFS or OS. In the Medical Research Council (MRC) AML-12 trial,51 1,243 patients aged 15 to 59 years (26 patients between 60-65 years of age) were randomly assigned either daunorubicin or mitoxantrone, each given cytarabine for one or two courses for induction. All patients achieving CR subsequently received multiple courses of consolidation chemotherapy. There were no significant differences in CR, percentage of patients dying in CR, resistant disease, relapse, DFS, or OS between the two induction regimens. The EORTC and GIMEMA conducted a prospective trial of either daunorubicin, mitoxantrone, or idarubicin combined with cytarabine and etoposide in standard doses for induction in younger patients followed by 500 mg/m² of cytarabine every 12 hours for 6 days plus the same anthracycline as given induction, as consolidation.52 There was no difference in CR rate, induction mortality rate, DFS, or OS among the three induction arms. Therefore, there is no evidence that one anthracycline is better than another for induction in older adults. In younger adults, emerging data suggest the same conclusion.

**Randomized Trials of Cytarabine Dose in Induction Therapy**

Cytarabine is one of the most active single drugs for the treatment of AML. Increased doses of cytarabine in induction have been explored. In a prospective randomized trial conducted at a single institution,53 intermediate-dose cytarabine at 500 mg/m² given with daunorubicin at 60 mg/m² provided similar results to conventional-dose cytarabine at 200 mg/m² with respect to CR rates (74% in the intermediate-dose arm and 71% in the conventional-dose arm) and DFS. Patients receiving the higher dose of cytarabine had a higher CR rate after one course of induction, but this was not statistically significant.

A number of studies have shown that HiDAC is effective treatment for patients with relapsed and refractory leukemia. Therefore, several trials have tested the benefits of HiDAC in induction (Table 4). Two prospective randomized trials that accrued relatively large numbers of patients compared HiDAC with standard induction while employing the same postremission therapy in both arms. The Australian Leukemia Study Group (ALSG)54 compared g/m² of HiDAC every 12 hours for 8 days on alternate days plus 50 mg/m² of daunorubicin and 75 mg/m² of etoposide to conventional induction with etoposide. The Southwest Oncology Group (SWOG)55 compared 2 g/m² of cytarabine every 12 hours for 6 days plus daunorubicin at 45 mg/m² to conventional induction. Both trials failed to identified a higher CR rate with HiDAC compared with standard induction, but the high-dose regimen was associated with increased hematologic and extra-medullary toxicity, including nausea, emesis, and ophthalmologic toxicity. In one of these studies, patients randomized to HiDAC had increased cerebellar toxicity. Both studies showed a longer DFS (but not OS) among patients receiving the high-dose regimen. However, these studies do not provide information as to whether HiDAC must be given in induction or if it would yield similar outcome results if given as consolidation.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Complete Remission (%)</th>
<th>5-Year Disease-Free Survival (%)</th>
<th>5-Year Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>H</td>
<td>P value</td>
<td>S</td>
</tr>
<tr>
<td>Weick55</td>
<td>493</td>
<td>172</td>
<td>58</td>
<td>55</td>
</tr>
<tr>
<td>Bishop54</td>
<td>152</td>
<td>149</td>
<td>74</td>
<td>71</td>
</tr>
<tr>
<td>Schiller53</td>
<td>51</td>
<td>50</td>
<td>71</td>
<td>74</td>
</tr>
</tbody>
</table>

HiDAC = high-dose cytosine arabinoside
Randomized Trials of Additional Drugs During Induction Therapy

The ALSG compared standard-dose cytarabine plus daunorubicin (7 + 3) to 7 + 3 plus etoposide at 75 mg/m² per day for 7 days (7 + 3 + 7) followed by consolidation with the same agents over a shorter time, 5 + 2 vs 5 + 2 + 5. Patients then received maintenance with cytarabine and 6-thioguanine for 2 years. Although there was a significantly longer DFS on the etoposide arm, OS was not improved. Updated results reveal that the median OS was not significantly improved on 7 + 3 + 7 compared with 7 + 3 (13 months vs 9 months, P=0.24). The 5- and 10-year OS rates for 7 + 3 + 7 were 19% and 16%, respectively, compared with 16% and 12%, respectively, for 7 + 3. However, the OS among patients less than 55 years of age was significantly longer on the 7 + 3 + 7 arm (P=0.04) with 5- and 10-year OS rates of 25% and 25%, respectively, and 17% and 14%, respectively for 7 + 3. Older patients experienced significantly more toxicity and no benefit in outcome. Therefore, in younger patients, intensified induction may improve CR duration and OS without necessarily improving the CR rate. However, caution in interpretation is required, given that there was no stratification at randomization based on age.

Updated results of the HiDAC + 3 + 7 vs 7 + 3 + 7 trial conducted by the ALSG show that the median remission duration was 46 months for HiDAC + 3 + 7 and 12 months for 7 + 3 + 7 (P=0.0007). The DFS rate among patients achieving CR at 5 years was 48% on the HiDAC arm compared with 25% on the 7 + 3 + 7 arm, and there were no relapses on either arm beyond 54 months. The difference in OS between the two arms approached statistical significance (P=0.053). These data suggest that intensified induction, as administered here, may improve outcome.

Sequential Standard-Dose Cytarabine Followed by High-Dose Cytarabine in Induction Therapy

Induction can also be intensified by adding HiDAC during the 3 days immediately following standard-dose cytarabine plus daunorubicin induction. Mitus and colleagues administered HiDAC on days 8, 9, and 10 of induction to exploit potential recruitment into the cell cycle and to avoid administrating an entire second cycle of induction for patients with residual leukemia after a first cycle. CR was achieved in 89% of patients, and essentially all patients achieved CR after one cycle of chemotherapy. Both ECOG and SWOG have completed phase II studies testing this strategy. No difference was observed in the CR rate among patients given the intensified induction compared to historical results with standard induction in either trial. The German AML Cooperative Group randomized newly diagnosed patients to either two courses of standard-dose cytarabine with daunorubicin and 6-thioguanine or one course of the same chemotherapy followed by HiDAC with mitoxantrone on day 21 regardless of the marrow findings. There were no differences in the CR rates (65% in the standard-dose vs 71% on the HiDAC arm, P=ns), in the induction death rate (18% vs 14%, P=ns), or in the relapse-free survival at 5 years (29%
vs 35%, \( P=ns \)). However, high-risk patients (i.e., more than 40% residual blasts on D16 marrow, unfavorable karyotype, and elevated LDH) had a higher CR rate (65% vs 49%, \( P=0.004 \)), a superior event-free survival rate at 5 years (17% vs 12%, \( P=0.012 \)), and a median OS at 5 years (13 months vs 8 months, \( P=0.009 \)).

**Hematopoietic Growth Factors During Induction Therapy**

Hematopoietic growth factors have been shown to shorten the period of neutropenia after induction therapy in AML (Table 5). Many prospective randomized trials have been conducted, but they vary with respect to design, patient age, and induction regimen. In the ECOG trial, patients between ages 55 and 70 received daunorubicin at 60 mg/m\(^2\) plus cytarabine at 100 mg/m\(^2\) for 7 days. The CR rate was better in the GM-CSF arm (60%) compared with the placebo arm (44%) (\( P=0.08 \)) and median times were significantly shorter on the GM-CSF arm.\(^6^4\) Furthermore, infectious toxicity was significantly reduced on the GM-CSF arm (\( P=0.015 \)). In an intent-to-treat analysis considering all randomized patients, the median survival was significantly longer for patients receiving GM-CSF (10.6 months vs 4.8 months). This difference was attributable to increased early mortality in the placebo group. The design of the CALGB trial reported by Stone and colleagues\(^6^8\) differed from the ECOG trial in that patients received GM-CSF or placebo on day 8 (vs day 11 in the ECOG study) immediately after completion of induction therapy, regardless of whether marrow aplasia was present. Due to perceived toxicity, 30% of patients discontinued the study drug in either arm. There was no difference in CR rates among patients assigned to GM-CSF vs placebo (51% vs 54%, \( P=0.61 \)). No differences were seen between the two groups in the incidence of both severe and lethal infection and the incidence of regrowth of leukemia. The median duration of neutropenia was only minimally shorter among patients receiving GM-CSF (15 days vs 17 days, \( P=0.02 \)). All studies demonstrated a shorter period of myelosuppression. In a study conducted in France,\(^6^5\) CR increased but survival was not prolonged. Neither

**Table 5. — Randomized Trials of Growth Factors After Induction Therapy in AML**

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Growth Factor</th>
<th>Start Day</th>
<th>Marrow Aplasia</th>
<th>CR (%)</th>
<th>Median Days ANC to 1000/µL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowe(^{64})</td>
<td>117</td>
<td>GM-CSF</td>
<td>11</td>
<td>Yes</td>
<td>60 vs 44</td>
<td>12 vs 18*</td>
</tr>
<tr>
<td>Dombret(^{65})</td>
<td>173</td>
<td>G-CSF</td>
<td>8</td>
<td>No</td>
<td>63 vs 32*</td>
<td>21 vs 27*</td>
</tr>
<tr>
<td>Heil(^{66})</td>
<td>521</td>
<td>G-CSF</td>
<td>8</td>
<td>No</td>
<td>69 vs 68</td>
<td>5 days**</td>
</tr>
<tr>
<td>Godwin(^{67})</td>
<td>234</td>
<td>G-CSF</td>
<td>11</td>
<td>Yes</td>
<td>42 vs 49</td>
<td>3-4 days**</td>
</tr>
<tr>
<td>Stone(^{68})</td>
<td>379</td>
<td>GM-CSF</td>
<td>8</td>
<td>No</td>
<td>52 vs 54</td>
<td>15 vs 17*</td>
</tr>
<tr>
<td>Zittour(^{69})</td>
<td>53</td>
<td>GM-CSF</td>
<td>8</td>
<td>No</td>
<td>48 vs 77*</td>
<td>Not different</td>
</tr>
<tr>
<td>Löwenberg(^{70})</td>
<td>316</td>
<td>GM-CSF</td>
<td>1-8</td>
<td>No</td>
<td>56 vs 55*</td>
<td>26 vs 31*</td>
</tr>
<tr>
<td>Link(^{71})</td>
<td>187</td>
<td>G-CSF</td>
<td>9</td>
<td>No</td>
<td>60 vs 43*</td>
<td>12 vs 18*</td>
</tr>
<tr>
<td>Goldstone(^{72})</td>
<td>800</td>
<td>G-CSF</td>
<td>8</td>
<td>No</td>
<td>72 vs 75</td>
<td>15 vs 20</td>
</tr>
<tr>
<td>Witz(^{73})</td>
<td>209</td>
<td>GM-CSF</td>
<td>1</td>
<td>No</td>
<td>63 vs 61</td>
<td>22 vs 26*</td>
</tr>
</tbody>
</table>

* \( P \leq 0.05 \)
** Recovery was faster with G-CSF by 3-5 days. Dates not stated.
CR = complete remission
ANC = absolute neutrophil count

the CALGB study nor the SWOG study showed that a shorter period of myelosuppression resulted in improvement in either the CR rate or OS. There is level I, grade A evidence from 10 prospective randomized trials that hematopoietic growth factors do shorten the period of neutropenia following induction chemotherapy but with little evidence of a significant improvement in outcome.

In the aggregate experience, these studies suggest that growth factors shorten the period of neutropenia following induction chemotherapy and, in several studies, significantly reduce morbidity. However, the CR rate and OS are generally not improved. Therefore, growth factors appear safe with little or no risk of leukemic cell stimulation.

Postremission Therapy

A variety of approaches have been explored to prevent relapse. Such strategies have included low-dose maintenance therapy, intensive consolidation therapy, or high-dose chemotherapy or chemoradiotherapy, with either allogeneic or autologous bone marrow or stem cell transplantation.

Maintenance Therapy

A prospective randomized trial conducted by ECOG suggested that maintenance therapy with 6-thioguanine plus cytarabine at 60 mg/m² once a week for 2 years offered a benefit in remission duration compared with no maintenance treatment (median remission duration of 8.1 vs 4.1 month, \( P=0.003 \)), although no significant survival difference was identified. In another prospective randomized ECOG trial, repeated courses of low-dose cytarabine were compared to observation as maintenance therapy after induction of a second CR in patients with relapsed or refractory AML (Fig 2). The median DFS among 41 patients assigned to low-dose cytarabine was 7.4 months compared to 3.3 months for the 45 patients receiving no additional treatment \( (P=0.084) \). However, the OS among the two groups was not different \( (10.9 \text{ months vs } 7.0 \text{ months}, \ P=0.615) \). Buchner and colleagues recently analyzed long-term follow-up data and observed a benefit to monthly maintenance for 3 years \( (5\text{-year DFS rate of } 23\% \text{ vs } 6\%) \). In an EORTC-HOVON trial, 76 patients aged 61 years or more achieving CR were randomized to no further therapy and 75 patients to eight cycles of low-dose cytarabine \( (10 \text{ mg/m² subcutaneously}) \) every 12 hours for 12 days every 6 weeks following consolidation with the same agents used in induction. An advantage in DFS was observed among patients receiving maintenance low-dose cytarabine every 6 weeks for 1 year \( (\text{median DFS rate was } 20\% \text{ vs } 7\% \text{ and } 5\text{-year DFS rate was } 13\% \text{ vs } 7\%, \ P=0.006) \). However, OS was not different \( (5\text{-year OS rate was } 18\% \text{ vs } 15\%, \ P=0.29) \).

![Fig 2. — Kaplan-Meier estimate for leukemia-free survival for patients with relapsed or refractory AML who achieved a second remission than were randomized to either low-dose cytarabine maintenance therapy or no additional therapy. From Robles C, Kim KM, Oken MM, et al. Low-dose cytarabine maintenance therapy vs observation after remission induction in advanced acute myeloid leukemia: an Eastern Cooperative Oncology Group Trial (E5483). Leukemia. 2000;14:1349-1353. Reprinted with permission.](image-url)
MRC in the United Kingdom randomized patients in CR to maintenance treatment for 1 year with 8 courses of cytarabine at 70 mg/m² given subcutaneously every 12 hours and 6-thioguanine at 100 mg/m² given orally every 12 hours for 5 days per month followed by four courses of cyclophosphamide, vincristine, cytarabine, and prednisone (COAP) or observation. With this therapy, relapse was delayed but not prevented, with no improvement in the OS at 5 years. Therefore, contemporary studies employing various maintenance regimens consistently show a benefit in DFS but not OS (level 1, grade B evidence).

**Intensive Consolidation Chemotherapy**

Phase II nonrandomized studies and retrospective analyses of cooperative group studies have suggested that increasing the intensity of postremission therapy is beneficial. Several studies have prospectively evaluated the role of intensive postremission consolidation with HiDAC. The CALGB randomly assigned 596 patients in CR to receive four courses of cytarabine at one of three doses: 100 mg/m² per day by continuous IV infusion for 5 days; 400 mg/m² per day by continuous IV infusion for 5 days; and 3 g/m² as a 3-hour IV infusion twice daily on days 1, 3, and 5 (Fig 3). High rates of central nervous system toxicity were observed in patients older than 60 years of age randomized to the high-dose regimen. Randomization was subsequently limited to patients 60 years of age or younger. The DFS rate was 21% in the 100-mg arm, 25% in the 400-mg arm, and 39% in the 3-g arm. The results were most significant in patients with favorable cytogenetics. This trial demonstrated a dose-response effect for cytarabine in patients undergoing postremission therapy. Although the HiDAC regimen used in this trial has become widely adopted, it should be noted that after the four courses of cytarabine, all patients received 4 monthly cycles of cytarabine at 100 mg/m² every 12 hours for 5 days by subcutaneous injection and daunorubicin at 45 mg/m² IV infusion on day 1. Remissions achieved in this trial were durable, with few relapses after 20 months. In an ECOG trial, patients without HLA-matched siblings were randomized to 2 years of continuous outpatient maintenance therapy with cytarabine and 6-thioguanine or a single course of intensive consolidation with cytarabine at 3 g/m² IV every 12 hours for 12 doses followed by 100 mg/m² of amsacrine per day IV for 3 days. The 4-year event-free survival rate was 27% for the intensive consolidation arm and 16% for the maintenance arm (P=0.068). This difference was statistically significant in patients younger than 60 years of age. The number of HiDAC courses required for optimal postremission therapy is uncertain.

The Finnish Leukemia Group randomized patients less than 65 years of age in CR after two courses of induction to either four additional consolidation courses after two courses of HiDAC-containing consolidation or to observation. No benefit was observed for...
patients randomized to the longer consolidation program, suggesting early intensive consolidation is likely the most important influence on outcome rather than the number of cycles of intensive chemotherapy.

Prospective Studies of Intensive Postremission Chemotherapy, AlloBMT, and AutoBMT

Several studies have compared prospectively the benefits of intensive consolidation with HiDAC, autologous bone marrow (or stem cell) transplantation, and allogeneic HLA-matched bone marrow transplantation (BMT). Autologous stem cell transplantation involves the administration of higher chemotherapy doses, but it is limited by the lack of the graft-vs-leukemia effect associated with allogeneic transplantation. Furthermore, there is a theoretic risk of infusion of occult residual leukemic cells. Allogeneic transplantation provides the best antileukemic potential, but it is consistently associated with a higher risk of treatment-related mortality than the other two strategies. All of these studies have assigned younger patients with an HLA-matched donor to allogeneic transplantation and randomized other patients to either consolidation chemotherapy or autologous transplantation or between the latter two strategies (Table 6). The earliest study carried out as a collaboration between the EORTC and GIMEMA included patients with a CR: 168 patients in first CR were assigned to allogeneic transplantation, and 254 were randomly assigned to one of the other two groups — 126 were randomized to a second cycle of consolidation with cytarabine at 2 g/m² every 12 hours on days 1-4 plus daunorubicin at 45 mg/m² on days 5-7, and 128 patients were randomized to autologous transplantation with cyclophosphamide/total body irradiation (TBI) or busulfan/TBI (55% of patients) as the preparative regimen. Only 74% of patients randomized to autologous transplantation actually completed the treatment because of early relapse and toxicity. Nevertheless, the DFS rate at 4 years, by an intent-to-treat analysis, was approximately 50%. This outcome is similar to that achieved among patients undergoing allogeneic transplantation (cyclophosphamide/TBI in approximately 66% of patients as the preparative regimen and busulfan/cyclophosphamide in 34%) who had a DFS of 55% rate at 4 years. These results were significantly better than those observed among patients receiving consolidation (30%). However, the OS at 4 years for all three treatment groups was similar (59% allogeneic, 56% autologous, and 46% consolidation). While relapse was more frequent among patients randomized to autologous transplantation, treatment-related mortality was higher among those assigned allogeneic transplantation.

Despite a similar trial design (although the autologous transplants were carried out with purged bone marrow), different observations were made in the trial conducted by ECOG, SWOG, and CALGB. The DFS rate associated with allogeneic transplantation was not significantly longer (43% at 4 years) than that associated with autologous transplantation (34%) or consolidation with HiDAC (34%). However, OS following HiDAC was longer than that after autologous or allogeneic transplantation. The discrepancy between DFS and OS likely relates to the opportunity to undergo transplantation at relapse among patients initially assigned consolidation chemotherapy.

In a study by Harousseau et al., there was no difference in the 4-year DFS or OS between patients randomized to autologous transplantation and those randomized to

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consolidation. The trial conducted by the MRC was unique because it demonstrated that the addition of autologous transplantation following three cycles of consolidation (two similar to induction and one including cytarabine at 1 g/m² every 12 hours for 3 days) reduced the risk of relapse and a statistical effect was seen on OS.65

The interpretations of these studies require caution. First, in all studies, a significant number of patients randomized to autologous transplantation do not receive the assigned treatment. Second, allogeneic transplantation offers the potential for graft-vs-leukemia effect and is associated with the lowest risk of relapse. However, higher treatment-related mortality compared with autologous transplantation and consolidation chemotherapy diminishes the impact of the greater antileukemic potential and thus a benefit in OS is not observed. Third, it is likely that the mortality rate associated with both autologous and allogeneic transplantation will continue to decrease as the techniques of transplantation improve, such as the introduction of autologous peripheral blood stem cell transplantation and improvements in T-cell depletion techniques for allogeneic transplantation.86,87 Furthermore, recent studies suggest that the outcome for allogeneic transplantation in patients older than age 40 may not be worse than for younger patients.49 There are improvements in all three postremission strategies that require frequent reappraisal of the benefits and hazards of each approach.72,89

### Treatment for Acute Promyelocytic Leukemia

Acute promyelocytic leukemia (APL) is treated differently from all other subtypes of AML and has become the most curable subtype of AML in adults. Phase II trials have confirmed the effectiveness of the vitamin A derivative all-trans retinoic acid (ATRA) as differentiation therapy in patients with APL.90-99 Two prospective randomized trials have compared ATRA with or without chemotherapy to chemotherapy alone for induction.100-101 Following CR, patients in both trials received two cycles of consolidation (7 + 3 followed by intermediate-dose cytarabine plus daunorubicin in the APL-91 trial100 and 7 + 3 followed by HiDAC plus daunorubicin in the North American Intergroup trial101). In the latter trial, patients in CR after two cycles of consolidation were randomized either to either 1 year of maintenance with ATRA or to observation. In both trials, the CR rates on both arms were not statistically different. However, event-free survival, DFS, and OS were markedly improved with ATRA such that approximately 70% of patients remain disease-free at 4 years. This benefit was attributable to a decrease in the relapse rate with ATRA. In the North American Intergroup trial, patients induced with standard induction chemotherapy and maintained with ATRA had an outcome identical to patients who received ATRA during induction. The most serious and life-threatening complication of differentiation therapy with ATRA is the retinoic acid syndrome, a cardiorespiratory distress syndrome manifested by interstitial pulmonary infiltrates, pleural or pericardial effusions, hypoxemia, and episodic hypotension with otherwise unexplained weight gain.102,103 The syndrome may be related to the rapid development of hyperleukocytosis, which can be observed with ATRA induction. The syndrome usually resolves quickly if corticosteroids (10 mg of dexamethasone b.i.d. for at least 3 days) are administered at the earliest sign or symptom. The APL-93 trial showed that administering concurrent ATRA plus chemotherapy reduces the relapse rate compared to sequential ATRA for induction followed by chemotherapy.104 This was observed even among patients presenting with a relatively low white blood cell count. Therefore, the standard induction strategy for APL now includes ATRA plus chemotherapy for all patients.

The MRC randomized patients either to a 5-day short course of ATRA (to reduce the coagulopathy but avoid the retinoic acid syndrome) before commencing chemotherapy or to concomitant ATRA and chemotherapy until initial CR.105 The latter strategy was associated with an improved outcome. Although the best chemotherapy regimen to include in induction is not established, anthracycline alone during induction is sufficient.105-109 The best consolidation regimen has not been established; however, it appears that all patients should receive at least two cycles of consolidation with either anthracycline plus cytarabine (as in the APL-91 trial), anthracycline plus...
cytarabine followed by HiDAC (as in the North American Intergroup Trial), or intermediate-dose cytarabine plus idarubicin followed by mitoxantrone, etoposide, cytarabine, and 6-thioguanine (as in the GIMEMA trial). Anthracyclines alone as consolidation may well be sufficient. The precise role of maintenance therapy with ATRA continues to evolve. The North American Intergroup Trial and the APL-93 trial both suggest a beneficial role.

Treatment of Older Adults

The treatment of older adults with AML is problematic, and the results are disappointing. Older patients do not tolerate intensive chemotherapy as well as younger patients. In addition, older adults with AML frequently have leukemic cells with poor prognosis karyotypes. Finally, such patients have leukemic cells that frequently express the MDR marker P-glycoprotein, which renders their cells more resistant to chemotherapy than the cells of younger patients.

An EORTC trial randomized patients older than 65 years of age either to immediate intensive induction chemotherapy or to supportive care with the introduction of mild cytoreductive chemotherapy for relief of leukemia-related symptoms. An improved survival was noted for patients receiving initial intensive chemotherapy (21 weeks vs 11 weeks, P = .015). Some investigators have recommended low-dose cytarabine as a putative differentiating agent since this approach is less toxic and may induce CR in up to 50% of patients, as reported in a small series. However, the drug likely acts as a cytotoxic agent, and this treatment is associated with significant morbidity and mortality. Most series report CR rates of 15%-23%. Stasi and colleagues reported that among 92 patients age 60 or older suitable for aggressive chemotherapy, the CR rate was 52%. The median CR duration was 35 weeks and event-free survival was 27 weeks. In their multivariate analysis, the three risk factors predictive of a longer event-free survival were abnormal karyotype, CD14 expression on leukemic cells, and age older than 67 years. Bow and co-investigators evaluated a combination of mitoxantrone and etoposide as remission induction in older adults. A CR rate of 55% was achieved with an induction mortality rate of 12%.

Primary Therapy of AML for Patients Outside of Clinical Trials

For patients 55 years of age or less, standard induction includes either daunorubicin or idarubicin and cytarabine. Hematopoietic growth factors may be administered safely following induction. If an HLA-compatible sibling is available, allogeneic BMT can be considered, either immediately after induction or after a single cycle of intensive postremission therapy that may include cytarabine at 3 g/m² every 12 hours for 6 days or 3 g/m² twice daily on days 1, 3, and 5. In an International Bone Marrow Transplant Registry analysis, no benefit in outcome after HLA-matched sibling transplantation was observed for any dose of consolidation chemotherapy following successful remission induction. If no HLA-compatible sibling is available, postremission therapy is given either with one cycle of cytarabine, as above, with an autologous stem cell transplant using peripheral blood derived stem cells or with four cycles of cytarabine if an autologous stem cell transplant is not to be carried out.

For patients over 55-65 years of age, induction with either daunorubicin and idarubicin or mitoxantrone and cytarabine is given followed by consolidation with cytarabine at 1.5 g/m² every 12 hours for 6 days for 1-2 cycles. Autologous stem cell transplantation may be considered if concurrent medical problems do not preclude such an approach. For patients older than 69 years of age, the dose of postremission cytarabine may be reduced to 1.5 g/m² for 6 doses. Maintenance therapy with low-dose cytarabine may be valuable.

Specific karyotype abnormalities, as well as other risk factors including age and comorbid illness, may influence the therapeutic decisions. For example, patients with favorable karyotypes may fare particularly well with intensive consolidation or transplant. The outcome of patients with unfavorable karyotypes is poor with intensive cytarabine consolidation.
fore, allogeneic transplantation should be considered. Improvements in both consolidation chemotherapy and stem cell transplantation will require frequent re-evaluation to identify the best strategy for postremission therapy for a given patient population.

Patients with newly diagnosed APL should be treated with ATRA and concurrent chemotherapy. The best chemotherapy to administer in induction has not been established but may include only an anthracycline, either daunorubicin or idarubicin. Higher doses, such as daunorubicin at doses of at least 50-60 mg/m² per day for 3 days, can be considered. Once CR is achieved, ATRA can be discontinued, and 2-3 cycles of anthracycline-rich consolidation chemotherapy are administered. An anthracycline alone may be sufficient. The role of ATRA during consolidation remains to be determined. Molecular studies are carried out at the end of consolidation and then serially in order to detect early relapse. Maintenance therapy, either with ATRA or with ATRA plus low-dose chemotherapy with 6-mercaptopurine and methotrexate, appears to be beneficial in preventing relapse.

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