Cytarabine Plus Idarubicin or Daunorubicin as Induction and Consolidation Therapy for Previously Untreated Adult Patients With Acute Myeloid Leukemia

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The purpose of this study was to determine the relative merits of idarubicin and daunorubicin in acute myeloid leukemia (AML) therapy. Thirty-two sites provided 214 previously untreated adults with AML aged 15 years or more who were randomized to receive induction therapy with cytarabine 100 mg/m²/d as a continuous 7-day infusion plus either daunorubicin 45 mg/m²/d (A + D) or idarubicin 13 mg/m²/d (A + I), daily on the first three days of treatment. Postremission therapy consisted of two courses of the induction regimen at the same daily doses, with the anthracycline administered for 2 days and cytarabine for 5. The complete response (CR) rates for evaluable patients were 70% (A + I) and 59% (A + D) (P = .08). The difference in CR rates was significant in patients aged 18 to 50 years (88% for A + I, 70% for A + D, P = .035). Resistant disease was a significantly more frequent cause of induction therapy failure with A + D than with A + I. Hyperleukocytosis (white blood cell count > 50,000/µL) unfavorably affected the attainment of CR with A + D but not with A + I. CR duration was significantly greater after A + I treatment, and the survival of all randomized patients treated with A + I was significantly better than that observed after A + D treatment (median 12.9 months vs 8.7 months, respectively, P = .038). Toxicity of the two treatments was similar, although A + I patients experienced more prolonged myelosuppression during consolidation therapy, and a greater incidence of mild chemical hepatitis was observed in the A + I group. It is concluded that, at the doses and schedule used in this study, A + I is superior to A + D for induction therapy of AML in adults.

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MATERIALS AND METHODS

Patient population and treatment. From November 25, 1985 to January 9, 1989 a total of 214 adults with previously untreated AML from 32 institutions in the United States were randomized to receive induction therapy with cytarabine 100 mg/m²/d administered as a continuous 7-day infusion plus either daunorubicin 45 mg/m²/d administered as a bolus intravenous injection on each of the first 3 days of treatment (A + D) or idarubicin 13 mg/m²/d administered on the same schedule as daunorubicin (A + I). Patients who failed to achieve CR were offered a second course of treatment with the same dosages as the first. Patients were stratified by age during randomization (18 to 50 years, 51 to 60 years, and greater than 60 years). Patients who received prior chemotherapy or radiotherapy, or who had a prior malignancy other than cutaneous basal cell carcinoma were ineligible for the study. Patients with a prior diagnosis of myelodysplasia, preleukemia, or refractory anemia were eligible but only a small number of such patients were actually entered (Table 1). In addition, patients with significant hepatic or renal dysfunction were ineligible, as were patients with a recent myocardial infarction (within 6 months) or a left ventricular ejection fraction greater than 10% below the lower limit of normal for each participating institution.

Postremission therapy consisted of two courses of the induction regimen in which idarubicin was substituted for daunorubicin in the two treatments in induction therapy for adults with previously untreated AML.

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anthracycline, and cytarabine. Both were administered at the induction daily dose, but the agents were administered for 2 and 5 days, respectively.

CR was defined by standard criteria. Incomplete responses were considered failures.

Although supportive care was not standardized in the protocol, all investigators transfused platelets prophylactically for severe thrombocytopenia, and all administered empiric broad spectrum antibiotics for febrile episodes in granulocytopenic patients. Morphologic confirmation of the diagnosis and of French-American-British (FAB) classification was accomplished centrally by a review of stained and unstained peripheral blood and bone marrow slides submitted univariately for confirmation of the morphologic diagnosis. When necessary, submitted unstained slides were stained with Sudan Black B or Periodic Acid-Schiff Reagent and examined. In only one instance of AML was the diagnosis changed from AML to acute lymphocytic leukemia by this review. Otherwise, there was an 89% agreement between the treating physician and the central reviewer with respect to precise FAB type. Most of the disagreements concerned confusion among FAB M1 and M5 that were frequently resolved by review of special stains.

### RESULTS

#### Morphology review. 
Wright's stained bone marrow smears were reviewed centrally for confirmation of the morphologic diagnosis. When necessary, submitted unstained slides were stained with Sudan Black B or Periodic Acid-Schiff Reagent and examined. In only one instance was the diagnosis changed from AML to acute lymphocytic leukemia by this review. Otherwise, there was an 89% agreement between the treating physician and the central reviewer with respect to precise FAB type. Most of the disagreements concerned confusion among FAB M1 and M5 that were frequently resolved by review of special stains.

#### Treatment outcome. 
One hundred and one patients were randomized to induction therapy with A + I and 113 to A + D. Four patients randomized to A + I and two randomized to A + D were inevaluable for response. Two inevaluable A + I patients were randomized but never treated, one received a significant overdose of cytarabine, and one refused all bone marrow examinations. One inevaluable A + D patient did not have AML, and another received idarubicin at three times the protocol dose rather than daunorubicin. Therefore, 97 A + I and 111 A + D patients were evaluable for response to induction therapy. All randomized patients as treated were evaluated for induction therapy toxicity.

#### Importantly pretreatment patient characteristics are shown in Table 1. This was a relatively elderly study population with a median age of 55 years, and 40% of patients were older than age 60 years. The treatment groups were well balanced with respect to age, performance status, blood counts, FAB type, and the presence or absence of infection or hemmorhage before treatment. There were more patients entered in the A + I group with a prior hematologic disorder than in the A + D group (Table 1).

A CR was obtained in 67% of all patients randomized to A + I and 58% of those randomized to A + D. The CR rate for evaluable patients in both groups was 70% and 59%, respectively (P = .08 (Table 2). Age had a major impact on response rate in both groups, and patients less than 60 years...
old had significantly higher response rates in both groups than patients aged 60 years or more. However, it is noteworthy that 46% of all patients over the age of 60 years achieved CR. It is noteworthy that 46% of all patients over the age of 60 years achieved CR. A + I resulted in a higher response rate than A + D in all evaluable patients, but the difference was most notable for patients ≤ 50 years of age (P = .035) (Table 3). CR to A + I occurred more frequently after one course than did responses to A + D (P = .015) (Table 2). The CR rates for the small number of evaluable patients with a prior hematologic disorder were similar in the two treatment groups (A + I, 60%; A + D, 43%).

Hyperleukocytosis, which has been reported to have an adverse effect on response rate, was examined for its effect on that parameter in this study. A CR was obtained in 52 of 75 (69%) of patients treated with A + I whose initial white blood cell (WBC) count was 50,000/μL or less, and in 13 of 19 (68%) of patients in that group with an initial WBC count greater than 50,000/μL. In the A + D treatment group, 58 of 89 (65%) patients with a WBC count of 50,000/μL or less obtained a CR, while only 7 of 22 (32%) patients with a higher WBC count did. Thus, A + I treatment may yield CRs in patients with hyperleukocytosis more frequently than treatment with A + D (P = .019).

The median time required to achieve an M1 marrow was 35 days for the A + I group and 36 days for the A + D group. However, an occasional patient in both groups required significantly longer to achieve M1 marrow status due to delayed recovery from drug-induced marrow hypoplasia.

Reasons for induction therapy failure are shown in Table 4. Resistant disease was more frequently a cause of failure in the A + D group than in the A + I group (P = .015).

Sixty-eight A + I and 66 A + D patients are evaluable for duration of response. The median duration of response was 9.4 months and 8.4 months, respectively. When the response duration curves were subjected to logrank analysis, a significant difference in favor of the A + I treatment emerged (P = .021) (Fig 1). Neither initial WBC count nor patient age had a significant effect on remission duration in either treatment group. In addition, remission duration was not significantly affected by the number of induction courses required (one or two) for CR in either treatment group.
omitting the second course in the A + D patients were: relapse (four patients), death during first consolidation course (one patient), refusal (one patient), significant decline in left ventricular ejection fraction (one patient), persistent fungal infection (one patient), development of a second malignancy (one patient developed colon cancer), and unknown (one patient). Four patients considered evaluable for this phase of therapy received considerably less therapy than required by protocol. Three patients (two in the A + I groups and one in the A + D groups) did not receive an anthracycline during this treatment phase because of a reduced left ventricular ejection fraction.

The survival of all randomized patients is depicted in Fig 2. Bone marrow transplant recipients were censored at the time of transplantation in that figure. The median survival for the A + I and A + D groups is 12.9 months and 8.7 months respectively, and logrank analysis of the survival curves indicates a significant survival advantage for the A + I group ($P = .038$). The median survival of all randomized patients greater than 60 years of age was equally poor in both treatment groups (3.4 and 3.2 months). However, the median survival for patients aged 18 to 60 years was better for the A + I group than for the A + D group (16.5 months and 10.7 months, respectively). Logrank analysis of the A + I and A + D survival curves for this age group (not shown) showed superiority for the A + I survival experience ($P = .03$).

The median survival of all CRs to A + I was 549 days (range, 32 to 1,150+ days). At the time of analysis, 12 of 68 (18%) CRs had survived more than 2 years and only 3 of the 12 have died. Twenty-two of the 66 CRs remain alive in continuous first remission. CRs to A + D had a median survival of 478 days (range, 31 to 1,368 days) and 5 of 66 (8%) have survived beyond 2 years, all of whom are still alive. Fourteen of 66 CRs to A + D remain alive in continuous first remission.

Because initial WBC count has been noted to influence overall survival in other studies, its relationship to survival was evaluated in this study. The median survival of the randomized patients treated with A + D whose initial WBC count was 50,000/µL or less was 323 days (range, 9 to 1,368+ days). Twenty-one patients were alive at the time of the analysis. The median survival of 23 evaluable patients treated with the same regimen whose initial WBC count was greater than 50,000/µL was 111 days (range, 12 to 575 days) and only two patients were alive at the time of analysis. The unfavorable effect of hyperleukocytosis on survival was muted in the A + I treatment group. The median survival of 79 randomized patients in that group whose initial WBC count was 50,000/µL or less was 364 days (range, 7 to 1,107+ days), with 29 patients alive at the time of analysis. The median survival of 19 A + I patients who presented with higher WBC counts was 340 days (range, 28 to 1,107+ days), with four patients alive at the time of analysis. Thus, A + I treatment provided a survival advantage over A + D treatment for patients who presented with hyperleukocytosis ($P = .008$).

Twelve patients in this study (nine for A + I, three for A + D) underwent autologous bone marrow transplantation during initial complete remission. Their ages ranged from 22 to 41 years. Three have died and nine remain alive 13.0 to 33.5+ months posttransplantation.

Toxicity of induction therapy. Toxicity of the two induction regimens was similar. Nausea occurred with equal frequency in both groups (82% of patients) and was primarily grade 1 or 2. Vomiting occurred more frequently in patients treated with A + D (66%) compared with those in the A + I group (57%), and anorexia was more common in the A + D groups (71% v 63% for A + I patients). Stomatitis (63%), esophagitis (13%), and diarrhea (78%) occurred with equal frequency and severity in the two groups and was generally mild. Fever occurred in all patients, and clinically or microbiologically documented infection (mean Eastern Cooperative Oncology Group [ECOG] grade = 2.7) was diagnosed in 89% of patients treated with A + I and 92% treated with A + D. Hemorrhage, usually mild, was recorded in 56% of all patients and occurred with equal frequency in the two study groups. Grade 3 or 4 alopecia developed in approximately 37% of patients in each group. Skin reaction was infrequent and minor. Five A + D patients (4%) experienced significant pain on injection of the anthracycline, while no A + I patient had that experience. Phlebitis of clinical concern developed in 7% of patients in both groups. Dysphagia (mean grade = 2.1) developed in 28% of A + I patients and 18% A + D patients.

The majority of patients in either group developed transient laboratory evidence of hepatic dysfunction that was usually self-limiting. No differences in frequency or severity of elevation in serum SGOT, alkaline phosphatase, or lactate dehydrogenase (LDH) were observed between the two groups, but a higher incidence of transient, mild hyperbilirubinemia ($>1.25$ times normal) occurred in A + I patients (59%) compared with A + D patients (45%). Mild elevations of blood urea nitrogen (BUN) and creatinine were recorded with equal frequency in the two groups and were of no clinical significance. The median maximum serum bilirubin level of 1.6 mg/dL for A + I-treated patients was significantly higher than the 1.2 mg/dL mean maximum elevation for A + D patients ($P < .01$).
Hematologic toxicity is shown in Table 5. No significant differences in the degree of WBC count or platelet count suppression occurred between the two treatment groups during induction therapy and the numbers of platelet and red blood cell (RBC) units transfused to patients in both treatment groups were similar during that phase of treatment.

Twenty-one patients in each group of evaluable patients died during induction therapy (Table 4). The majority of the patients who died had microbiologic and/or clinical evidence of bacterial or fungal infection at the time of death. One A + I patient died with acute hepatic necrosis after receiving allopurinol 300 mg three times daily for 3 weeks, and two A + D patients died of intracranial hemorrhage. The median ages of the A + I and A + D patients who died during induction therapy were 64 and 68 years, respectively, which was older than the median ages of all treated patients in the study.

A + I patients were hospitalized a median of 34 days for induction therapy (range, 0 to 106) and A + D patients were hospitalized a median of 35.5 days (range, 12 to 241). A + I patients received intravenous antibiotics for a median of 27.5 days (range, 7 to 73) and A + D patients received such treatment for a median of 26 days (range, 3 to 94).

Toxicity of consolidation therapy. Consolidation therapy was received by 52 A + I patients and 53 A + D patients. Nonhematologic toxicity during this treatment phase was less common and less severe than during induction therapy as would be expected. The frequency and severity of toxicity was similar in both treatment groups except for grade 1 to 2 pain with anthracycline injection, which occurred in 4% of A + D patients and no A + I patients, and mild dysphagia (grade 1 to 2), which occurred in 15% of A + I patients and none treated with A + D (P < .01). Hepatic enzyme elevations occurred with equal frequency and severity in both treatment groups except for grade 2 to 3 serum LDH elevation, which only occurred in the A + D groups (P = .009). However, the median serum bilirubin elevation was significantly higher in the A + I group (P < .05). Renal dysfunction occurred in a small minority of patients in both groups with equal frequency and was most likely related to the administration of other drugs.

Significantly greater WBC and platelet count suppression occurred in the A + I group during each of the two consolidation courses (P < .01) (Table 5). When the data for both consolidation courses are combined, A + I patients spent a median of 28 days in hospital compared with a median of 22 days for the A + D group, and A + I patients received intravenous antibiotics for a median of 15 days, compared with a median of 7 days for A + D patients.

To date, the incidence of congestive heart failure, arrhythmias, decreased left ventricular ejection fraction by ≥10%, and other serious cardiac events is negligible and similar for the two treatments. Two patients in each treatment arm died during consolidation therapy of sepsis while in CR. Three of those patients died during the second consolidation course and one (A + D arm) died during the first course.

### DISCUSSION

The observation in mice that idarubicin has significantly greater antileukemic activity than daunorubicin1 and results of phase II clinical trials showing efficacy for idarubicin in patients with AML warranted a comparative trial of idarubicin with its parent compound in previously untreated adult patients. The present study was designed to provide that comparison. Interim results have previously been published.17 The anthracyclines were administered on the same schedule in conjunction with a standard dose and schedule of cytarabine.2 The dose of daunorubicin is standard in this study2 and the dose of idarubicin was slightly higher (8%) than that used in conjunction with cytarabine administered at a greater total dose in a similar study at Memorial Sloan-Kettering Cancer Center.18 Because toxicities that resulted from both induction treatments in this study were essentially equivalent, it can be inferred that the doses of idarubicin and daunorubicin administered for induction therapy were equitoxic. It is, therefore, of interest that patients treated with A + I had a significantly greater response duration and survival compared with patients

### Table 5. Hematologic Toxicity

<table>
<thead>
<tr>
<th></th>
<th>A + I</th>
<th>A + D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of days WBC &lt; 1,000/μL</td>
<td>23 (0-764)</td>
<td>22.5 (0-240)</td>
</tr>
<tr>
<td>No. of days platelets &lt; 50,000/μL</td>
<td>24.5 (6-764)</td>
<td>29 (0-229)</td>
</tr>
<tr>
<td>No. of units platelets transfused</td>
<td>61 (0-298)</td>
<td>63.5 (0-290)</td>
</tr>
<tr>
<td>No. of units RBCs transfused</td>
<td>14 (0-43)</td>
<td>12 (0-44)</td>
</tr>
<tr>
<td>No. of days parenteral antibiotics</td>
<td>27.5 (7-73)</td>
<td>26 (3-94)</td>
</tr>
<tr>
<td><strong>Consolidation course 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of days WBC &lt; 1,000/μL</td>
<td>17 (0-239)</td>
<td>0 (0-22)</td>
</tr>
<tr>
<td>No. of days platelets &lt; 50,000/μL</td>
<td>19.5 (0-239)</td>
<td>14 (0-162)</td>
</tr>
<tr>
<td><strong>Consolidation course 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of days WBC &lt; 1,000/μL</td>
<td>18.5 (0-37)</td>
<td>0 (0-28)</td>
</tr>
<tr>
<td>No. of days platelets &lt; 50,000/μL</td>
<td>21.5 (0-44)</td>
<td>15 (0-66)</td>
</tr>
<tr>
<td><strong>Both consolidation courses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of units platelets transfused</td>
<td>24 (0-224)</td>
<td>10 (0-270)</td>
</tr>
<tr>
<td>No. of units RBCs transfused</td>
<td>6 (0-69)</td>
<td>4 (0-20)</td>
</tr>
<tr>
<td>No. of days parenteral antibiotics</td>
<td>15 (0-96)</td>
<td>7 (0-27)</td>
</tr>
</tbody>
</table>

Values are median (range). Unless otherwise noted, values for A + I versus A + D comparisons were not significantly different.
treated with A + D. In addition, there was a trend toward a greater CR rate and a significantly greater likelihood of achieving CR with one induction course of A + I. Furthermore, the adverse affect of hyperleukocytosis on response rate and survival was less evident with A + I treatment than with treatment with A + D.

An overview of idarubicin treatment for acute leukemia has recently been offered by Carella et al.10 Idarubicin and cytarabine have been studied in several schedules in patients with relapsed AML and the combination has been found to be effective with acceptable, expected toxicity.14,19-21 Lambertenghi-Delliliers et al2 treated 50 patients with previously untreated AML with idarubicin 12 mg/m²/d for 3 days, and cytarabine 240 mg/m² for 7 days and observed an 80% CR rate. Subsequently, five trials, including the present study, were conducted to compare the relative efficacy and toxicity of A + I and A + D. In two of the studies, only older patients were enrolled12,23 and there was no significant difference in outcome between the two treatments, except that in the study by Mandelli et al23 a significantly greater number of CRs achieved CR with one course of A + I than with one course of A + D, as in the present study. The difficulty in showing an advantage for one treatment over another in elderly patients with AML when such an advantage can be shown in younger patients was noted by Bishop et al.29 They could not show a survival advantage for a three-drug regimen compared with a two-drug regimen in older patients when a significant survival advantage for the former was evident in younger patients. Our results are consistent with the Bishop et al29 and Mandelli et al23 data in that the superiority of A + I compared with A + D was more evident in younger patients.

The results of the present study are essentially identical to those of Berman et al,18 who used cytarabine 200 mg/m² as a 5-day continuous infusion together with three daily bolus doses of idarubicin 12 mg/m² or daunorubicin 50 mg/m². In her study and ours, CR rate (patients ≤50 years of age), response duration, and survival were significantly better with A + I than with A + D. In addition, in both studies the majority of CRs to A + I achieved a response with one induction therapy course, whereas a minority of CRs to A + D achieved remission with one course of treatment. Furthermore, in both studies, hyperleukocytosis unfavorably effected response rate in the A + D groups, but not in the A + I groups. Mild hyperbilirubinemia was more common in the A + I group compared with the A + D group in both studies, and in both other toxicities of induction therapy were similar in frequency and severity. Toxicity of postremission therapy is not discussed in Berman et al,18 but in the present study postremission therapy with A + I was more myelosuppressive than A + D treatment. The results of Berman et al and the present study suggest that idarubicin doses of 12 and 13 mg/m² are equivalent antileukemia doses, as are 45 and 50 mg/m² daunorubicin doses.

In the study by Vogler et al29 cytarabine was administered at a dose of 100 mg/m² by continuous intravenous infusion for 7 days (as in the present study) and combined with either idarubicin 12 mg/m² (A + I) or daunorubicin 45 mg/m² (A + D) daily for 3 days. A significantly higher CR rate was observed with A + I treatment, but no significant difference in response duration or survival was noted between the two treatments.

The three comparative American studies17,18,26 suggest that A + I is a better treatment for previously untreated adults with AML than A + D. The CR rate was higher in all three studies for A + I and overall survival of the A + I group was significantly better in two.

In a study of similar design to the present study, Arlin et al27 compared A + D in the same dose and schedule as in the present study with mitoxantrone 12 mg/m²/d daily for 3 days substituted for daunorubicin in the regimen (A + M). Postremission therapy was of similar concept and design as in the present study. The investigators concluded that, because there were no significant differences between A + D and A + M with respect to CR rate or duration, survival, or toxicity, A + D and A + M were comparable in the first-line treatment of patients with AML. However, in that study a greater number of patients failed A + D due to persistent leukemia than did patients treated with A + M, and patients treated with A + M were more likely to achieve CR with one induction course than were patients treated with A + D.

It therefore appears that equitoxic A + I and A + M regimens are better therapy than A + D for the treatment of newly diagnosed patients with AML. The present study and others18,26 suggest that A + I may be superior to A + M because significant differences in outcome have been identified for A + I when directly prospectively compared with A + D, and no significant differences were noted between patients treated with A + D or A + M in a study of similar design.27 A direct, prospective comparison of A + D, A + M, and A + I would be of interest and is warranted.

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