Results of a Randomized Trial Comparing Idarubicin and Cytosine Arabinoside With Daunorubicin and Cytosine Arabinoside in Adult Patients With Newly Diagnosed Acute Myelogenous Leukemia

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4'-Demethoxydaunorubicin (idarubicin [IDR]) is a new anthracycline that differs from its parent compound by the deletion of a methoxy group at position 4 of the chromophore ring. This minor structural modification results in a more lipophilic compound with a unique metabolite that has a prolonged plasma half-life as well as in vitro and in vivo antileukemia activity. To determine its activity in acute myelogenous leukemia (AML), 130 consecutive adult patients between the ages of 16 and 60 with newly diagnosed disease were randomized in a single institution study to receive either IDR in combination with cytosine arabinoside (Ara-C) or standard therapy with daunorubicin (DNR) and Ara-C. The trial was analyzed using the O'Brien-Fleming multiple testing design that allowed for periodic inspection of the data at specific patient accession points. After accrual of 60 patients per arm, analysis showed that patients who received IDR/Ara-C had a superior response compared with those who received standard therapy: 48 of 60 patients (80%) achieved complete remission on the former arm compared with 35 of 60 patients on the latter (58%, P = .005). Logistic regression analysis of factors associated with complete response indicated that treatment with IDR/Ara-C offered a significant advantage to patients who presented with a high initial white blood cell count compared with treatment with DNR/Ara-C. The degree of marrow aplasia was approximately the same on each arm as was nonhematologic toxicity. Overall survival for patients on the IDR/Ara-C arm was 19.5 months compared with 13.5 months on the DNR/Ara-C arm (P = .025) at a median follow-up of 2.5 years. We conclude that IDR/Ara-C can effectively replace standard therapy with DNR/Ara-C in adult patients less than age 60 with newly diagnosed AML.

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OVER THE LAST DECADE, new drug development in the field of acute leukemia has yielded at least three agents worthy of further clinical evaluation. Drugs such as amsacrine,1,2 mitoxantrone,3,4 and 4-demethoxydaunorubicin (idarubicin [IDR])5,6 have all demonstrated important response rates for patients with acute myelogenous leukemia (AML). The synthetic anthracycline analogue IDR is of particular interest because the minor structural alteration at position 4 of the chromophore ring (Fig 1) allows for several unique properties of the parent compound and its primary metabolite. While the molecular mechanism of IDR does not appear to be qualitatively different from daunorubicin (DNR) in that both have equal affinity for isolated DNA7 and comparable inhibition of DNA polymerase and topoisomerase II,8 the modification at position 4 results in (1) a higher lipophilic coefficient and therefore more rapid cellular uptake9 and (2) induction of more DNA single strand breaks in tumor cells.10 In addition, IDR is metabolized to an active alcohol derivative, 13-hydroxyidarubicin, that has a prolonged plasma half-life12,13 and in vitro and in vivo activity equal to that of the parent compound.14,15

Phase I trials of IDR in patients with solid tumors demonstrated that the dose-limiting toxicity of the drug was myelosuppression and a dose of 12 mg/m2 was suggested for further Phase II testing.12,14 Simultaneously performed studies in Italy, France, and the United States demonstrated that IDR as a single agent induced complete remission (CR) in 13% to 22% of adult patients with relapsed or refractory AML when given at two-to-three times the solid tumor dose.5,14,16 When the drug was combined with cytosine arabinoside (Ara-C) the response rate increased to the range of 24% to 67% in similar groups of heavily pretreated patients.10,20

Memorial Hospital subsequently designed a prospectively randomized comparative trial to compare the efficacy of IDR and Ara-C (IDR/Ara-C) with that of standard therapy with DNR and Ara-C (DNR/Ara-C) in adult patients with newly diagnosed AML. The goals of this study were to evaluate the drug combinations with respect to (1) remission induction, (2) overall survival, (3) pre- and posttreatment cardiac function, and (4) factors associated with complete response and survival. This report details the results of that study.

PATIENTS AND METHODS

Study design. The initial randomized trial, the L-19 Protocol, began in 1984 and consecutively randomized all eligible adult patients between the ages of 16 and 60 with newly diagnosed AML to either IDR/Ara-C (IDR, 12 mg/m2/d for 3 days; Ara-C 25 mg/m2 (IV) bolus followed immediately by 200 mg/m2 given as a continuous infusion daily for 5 days); or DNR/Ara-C (DNR 50 mg/m2/d for 3 days; Ara-C as above) for induction therapy. Patients were not considered eligible for this study if they (1) had documentation of a
preexisting myelodysplastic syndrome for more than 3 months before entering a blastic phase, (2) had a secondary leukemia, or (3) presented in blastic phase of chronic myelogenous leukemia.

Patients who had persistent blasts on day 14 of study received a second identical induction course. Those who did not achieve remission after two cycles of therapy were considered failures and were removed from study.

Patients who achieved CR after one or two induction cycles received two courses of consolidation therapy, each 4 to 6 weeks apart. Consolidation consisted of the same drugs used during induction but given at slightly lower total doses (IDR 12 mg/m²/d for 2 days or DNR 50 mg/m²/d for 2 days; Ara-C 25 mg/m² IV bolus followed by 200 mg/m²/d given as a continuous infusion daily for 4 days). Patients under age 50 who had an HLA-identical sibling donor were offered autologous bone marrow transplantation usually after the first consolidation course. Patients not undergoing transplantation and remaining in remission after consolidation were subsequently randomized to either 1 year of maintenance therapy with low dose Ara-C (5 mg/m² subcutaneously twice per day for 14 days each month for 1 year) or no further therapy.

The L-19 Protocol accrued 50 patients before a major modification in postconsolidation therapy was introduced in 1986. Preliminary experience with autologous bone marrow transplantation performed in patients with AML in second or later relapse35,36 suggested that this might be a feasible approach for intense postconsolidation therapy in younger patients in first remission. We therefore altered the treatment approach after the first consolidation course such that the maintenance randomization was deleted and a purged autologous bone marrow transplant was offered to all patients under the age of 50 who had no HLA-identical sibling donor. Marrow was purged with 4-hydroperoxycyclophosphamide and etoposide (VP-16), frozen, and reinfused after conditioning with total body irradiation, high dose cyclophosphamide, and VP-16.22 This study, the L-22 Protocol, was therefore designed to continue data accrual on the induction randomization between IDR/Ara-C and DNR/Ara-C, and also to compare in a prospective fashion allogeneic and autologous bone marrow transplantation in first remission. The L-19 and L-22 Protocols are outlined in Fig 2.

All patients had a documented history and physical examination performed along with the following tests: complete blood count with differential, serum electrolytes, screening profile, blood urea nitrogen (BUN), creatinine, chest x-ray, electrocardiogram, and bone marrow samples for routine smear, cytochemical stains, and cytogenetic analysis. Patients also underwent a cardiac evaluation consisting of a resting gated heart scan to assess left ventricular function; scans were performed either before treatment began or within the first few days of therapy and follow-up scans were obtained in patients in remission after the last course of consolidation therapy.

All patients signed an informed consent before starting this study.

**Patient characteristics.** A total of 130 patients, 120 of whom were evaluable, were randomized. Table 1 outlines the patient characteristics in each group. The median age of the 120 evaluable patients was 37.5 years (range, 17 through 60); median age on the IDR/Ara-C arm was 37.5 years (range, 17 through 60) and median age on the DNR/Ara-C arm was 42 (range, 19 through 60). Fifty-nine of the patients were men and 61 were women. Initial blood counts at time of presentation as well as French-American-British (FAB) morphologic subtypes are also outlined in Table 1.

The number of patients considered to be at either good or poor risk for survival according to generally accepted criteria is also described according to treatment arm in Table 1. Good risk patients were those who had acute promyelocytic leukemia (FAB-M3) with or without the typical cytogenetic abnormality t(15;17)

**Fig 1.** Structure of Idarubicin and Daunorubicin.

**Fig 2.** IDR/Ara-C versus DNR/Ara-C in adult ANLL: Protocol outlines. (*) BM Day 14: If persistent blasts a second identical course is administered.

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>IDR/Ara-C</th>
<th>DNR/Ara-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (total/evaluable)</td>
<td>65/60</td>
<td>65/60</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>36 (17-60)</td>
<td>41 (19-60)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>27/33</td>
<td>28/32</td>
</tr>
<tr>
<td>Median WBC (range)</td>
<td>10.3 (6.4-149)</td>
<td>17.9 (0.7-230)</td>
</tr>
<tr>
<td>HGB (range)</td>
<td>9.2 (6.7-13.8)</td>
<td>9.2 (6.4-13.9)</td>
</tr>
<tr>
<td>PLTS (range)</td>
<td>53,500 (11-370,000)</td>
<td>65,500 (11-457,000)</td>
</tr>
<tr>
<td>FAB M—</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>9</td>
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<td>4</td>
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<td>13</td>
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<tr>
<td>5</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

"**Poor Risk**"**

- WBC >50,000 | 12 | 18 |
- (+) TdT      | 10 | 12 |
- (−) Auer Rods | 33 | 35 |

"**Good Risk**"

- t(8;21) | 2 | 1 |
- inv(16) | 1 | 3 |

*Patients may be included in more than one poor risk group.

†Patients included in a good risk group may also have had one poor prognostic factor; cytogenetic abnormality in this instance was considered the primary risk factor.
POOR RISK PATIENTS WERE THOSE WHO HAD THE FOLLOWING PRESENT AT TIME OF DIAGNOSIS: WHITE BLOOD CELL COUNT ABOVE 50,000, \textit{a} absence of Auer rods,\textsuperscript{23-30} and a positive enzymatic immunoassay for the enzyme terminal deoxynucleotidyl transferase (TdT) in either peripheral blood or bone marrow blasts.\textsuperscript{5-6}

\textbf{Remission and toxicity criteria.} Patients were considered to be in remission if they were asymptomatic, had no physical finding suggestive of extramedullary disease, and had two normocellular bone marrow samples at least one month apart demonstrating \(\leq 5\%\) blasts with normal erythropoiesis, granulopoiesis, and thrombopoiesis. The peripheral white blood cell count had to be at least 3,000/µL, the platelet count at least 100,000/µL, and the hemoglobin at least 10 g/dL for a minimum of 4 weeks.

Protocol failures were defined as (1) patients who died within 7 days of completing initial induction therapy (early death); (2) patients who died after day 7 of complications arising from marrow aplasia, usually hemorrhage or sepsis, before any remission status could be ascertained (aplastic death); or (3) patients who had \(> 5\%\) blasts after two induction courses (persistent blasts).\textsuperscript{37} All such patients are included in the study analysis.

Toxicity was characterized using standard World Health Organization criteria.\textsuperscript{38}

\textbf{Statistical design.} The primary goals of this prospectively randomized trial were to compare the proportion of adult patients who achieved remission on one arm versus the other and to determine factors associated with complete response. In addition, we wished to determine what, if any, pretreatment characteristics were associated with survival. Disease-free survival was not analyzed because of treatment-induced bias. That is, the more effective drug combination would induce remission in a greater proportion of patients at higher risk for failure, in which case comparison of disease-free survival curves could be biased against the more effective drug. Overall survival, however, would not be affected by this potential bias as the complete complement of randomized patients is included in this analysis regardless of response.

The O'Brien-Fleming multiple testing procedure was used to assess response to treatment.\textsuperscript{29} The test was designed to permit four analyses after successive groups of 20 patients per treatment arm were entered. To maintain an overall significance level of .05, the four analyses were conducted at the nominal significance levels of .001, .004, .019, and .043. The nominal significance levels and observed \(P\) values were calculated from the \(Z\) test statistic for the difference between two proportions.\textsuperscript{40} If the differences in the observed response proportions were significant at any one of the four testing points, the trial could be stopped at that point and a difference in the response proportion of the two populations could be declared.

The duration of survival was measured from the time of initial therapy to date of death or last follow-up (March 1990) and the probability of survival was calculated using the Kaplan-Meier estimate.\textsuperscript{41}

The following pretreatment characteristics were analyzed for response and survival using the likelihood ratio test statistic: age, initial white blood cell count, hemoglobin, platelet count, presence or absence of Auer rods, TdT, and specific cytogenetic abnormalities. Favorable cytogenetics included t(15;17), t(8;21) and inv(16)\textsuperscript{25-28}; other cytogenetic abnormalities, when present, were considered unfavorable. Any characteristic that demonstrated a potential association with either response or survival was subsequently analyzed using the logistic regression model when the endpoint was complete response, and the proportional hazards model when the endpoint was survival.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Stage & No. of Patients per Treatment Arm & Nominal Significance Level & \% Response IDW/Ara-C & DNR/Ara-C & Observed \(P\) Value & \hline
1 & 20 & .0001 & .85 & .55 & .134 & \\
2 & 40 & .004 & .85 & .58 & .006 & \\
3 & 60 & .019 & .80 & .58 & .005 & \\
4 & 90 & .043 & Trial stopped at Stage 3 & & & \\
\hline
\end{tabular}
\caption{O'Brien-Fleming Group Sequential Design Used in This Study}
\end{table}
A univariate analysis using the likelihood ratio statistic
for the interaction between treatment, WBC, and response
was also evaluated (Table 3). It is apparent from Table 3
that, when examined by number of courses needed to
achieve remission, there is no difference between the two
drug combinations with respect to normal marrow regen-
eration.

\[ \text{Days to CR (range)} = 33 (20-126) \]
\[ \text{Days to WBC > 1,000/\mu L} = 23 (11-59) \]

Prognostic variables associated with response to treatment.
A univariate analysis using the likelihood ratio statistic
indicated that both white blood cell count (WBC) and
treatment arm were important factors for achieving a
response (Table 4). However, in a multivariate analysis
using the linear logistic regression model, the relationship
between WBC and response changed after adjusting for
treatment effect (Fig 3); the calculated \( P \) value for this
interaction is \( .04 \). As shown in Fig 3, patients who were
randomized to IDR/Ara-C did well regardless of their
initial WBC, whereas the incidence of response decreased
as the WBC increased for patients on the DNR/Ara-C arm.
A descriptive summary of the interaction between treat-
ment arm and WBC is given in Table 5. The logistic
regression model is outlined in Table 6.

As outlined in Table 1, patients on the DNR/Ara-C arm
had, by chance, a higher median age and a higher incidence
of TdT-positive blasts. However, neither the inclusion of
age or TdT in the logistic regression model affected the
relationship between treatment, WBC, and response.

Table 1 also demonstrates that more patients on the
DNR/Ara-C arm had a high WBC. However, the logistics
regression model suggests that it is the WBC-treatment
interaction and not simply WBC alone that is significant in
determining response (Table 6).

Survival. The median follow-up for all patients on the
L-19 and the L-22 Protocols is 2.5 years (range, 7 months
to 4.8 years). Overall survival curves are given in Fig 4 and
demonstrate that patients on the IDR/Ara-C arm had
improved survival compared with patients on the DNR/
Ara-C arm (19.7 versus 13.5 months, \( P = .025 \)). Approximately
equal numbers of patients on each arm underwent
either maintenance therapy on the L-19 Protocol (IDR/
Ara-C arm: four patients, DNR/Ara-C arm: two patients)
or bone marrow transplantation (IDR/Ara-C arm: seven
patients, DNR/Ara-C arm: six patients). Factors associated
with an improved chance of survival were younger age,
favorable cytogenetics, treatment with IDR/Ara-C, and a
higher median age and a higher incidence of TdT-positive blasts. However, neither the inclusion of age or TdT in the logistic regression model affected the relationship between treatment, WBC, and response.
higher albumin level (Table 4). However, those patients with favorable cytogenetics also had a higher albumin level. Based on a multivariate analysis using the proportional hazards model, we conclude that the factors jointly associated with survival are age, cytogenetics, and treatment arm (Table 6).

In this series, WBC and TdT-positive blasts were not important factors for survival (Table 4). Although patients on the DNR/Ara-C arm had by chance a higher WBC and higher incidence of TdT-positive blasts (Table 1), these variables, when tested, did not alter the relationship between treatment and survival.

_Evaluation of postconsolidation therapy._ The first portion of this study randomized patients in remission to either 1 year of low-dose Ara-C or no further therapy. Thirty-three of the 48 patients who entered this portion of the study (L-19 Protocol) achieved remission with either IDR/Ara-C (20 of 25 patients) or DNR/Ara-C (13 of 23 patients). Twenty patients were eligible for the randomization between maintenance and no maintenance: four patients relapsed before reaching the randomization, five patients underwent allogeneic bone marrow transplantation, and four patients were lost to follow-up. Of the 20 patients who were actually randomized and eight refused randomization. No significant difference in survival was seen among the six patients who actually received maintenance therapy (median survival, 54 months) and the six patients that did not (median survival, 23 months; \( P = .37 \)).

Seventy-two evaluable patients were entered on the subsequent study, the L-22 Protocol, that offered autologous purged bone marrow transplantation to all patients under age 50 who did not have an HLA-identical sibling donor; patients who did have a matched donor sibling were offered allogeneic bone marrow transplantation (Fig 2). Forty-nine patients were under the age of 50 and thus were initially considered as potential bone marrow transplant recipients. However, only eight patients (16%) actually underwent the procedure (four patients had received IDR/Ara-C and four patients had received DNR/Ara-C). Reasons for this low transplant accrual rate are given in Table 7. Three patients remain alive and disease free in each of the transplant groups.

Nonhematologic toxicity. Nonhematologic toxicity data for induction are outlined in Table 8. No significant difference in the incidence or severity of nausea/vomiting, mucositis, or diarrhea was noted between the two arms. The incidence of abnormal liver function tests, as defined by a rise in bilirubin to greater than 2 mg/dL or an increase in serum glutamic-oxaloacetic transaminase (SGOT) to greater than 50 U was also equivalent on each arm. Twenty-eight patients who achieved remission on the DNRI Ara-C arm and 29 patients who achieved remission on the

### Table 5. Interaction Between Treatment Arm and WBC

<table>
<thead>
<tr>
<th>WBC ((\mu L))</th>
<th>No. of Patients</th>
<th>IDR/Ara-C</th>
<th>DNR/Ara-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2,900</td>
<td>30</td>
<td>12/15 (80%)</td>
<td>12/15 (80%)</td>
</tr>
<tr>
<td>2,900-13,700</td>
<td>30</td>
<td>15/17 (88%)</td>
<td>9/13 (69%)</td>
</tr>
<tr>
<td>13,700-48,000</td>
<td>30</td>
<td>12/16 (75%)</td>
<td>6/14 (43%)</td>
</tr>
<tr>
<td>&gt;48,000</td>
<td>30</td>
<td>9/12 (75%)</td>
<td>8/18 (44%)</td>
</tr>
</tbody>
</table>

### Table 6. Logistic Regression Model for Response

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Coefficient</th>
<th>Standard Error of Coefficient</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment*</td>
<td>-0.66</td>
<td>.476</td>
<td>.17</td>
</tr>
<tr>
<td>Treatment x WBC</td>
<td>-.012</td>
<td>.006</td>
<td>.04</td>
</tr>
<tr>
<td>Constant</td>
<td>1.38</td>
<td>.323</td>
<td></td>
</tr>
</tbody>
</table>

Proportional Hazards Model for Survival

- Treatment: 0 = IDR/Ara-C, 1 = DNR/Ara-C
- Age
- Cytogenetics†: 0 = unfavorable, 1 = favorable

*Treatment arm: 0 = IDR/Ara-C, 1 = DNR/Ara-C.
†Cytogenetics: 0 = unfavorable, 1 = favorable.
Table 8. Nonhematologic Toxicity

<table>
<thead>
<tr>
<th>Abnormal LFTs*</th>
<th>IDR/Ara-C</th>
<th>DNRAra-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood &gt; 2 g/dL</td>
<td>23/60 (38%)</td>
<td>16/60 (27%)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.2 (2.1-16.7)</td>
<td>4.5 (2.4-17.8)</td>
</tr>
<tr>
<td>SGOT &gt; 50 U</td>
<td>34/60 (57%)</td>
<td>34/60 (57%)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>111 (53-1,351)</td>
<td>143 (53-2,237)</td>
</tr>
<tr>
<td>Significant decrease in cardiac function (LVEF)</td>
<td>5/29 (17%)</td>
<td>5/30 (17%)</td>
</tr>
</tbody>
</table>

*LFTs: liver function tests. Normal bilirubin < 1.2 g/dL; normal SGOT < 25 U.
†Defined as > 10% absolute decrease in gated heart scan from pretreatment value.

DISCUSSION

Results of this study suggest that IDR/Ara-C can effectively replace DNR/Ara-C as standard therapy for adult patients under age 60 with newly diagnosed AML. In this prospectively randomized trial, more patients achieved remission on the IDR/Ara-C arm, the majority did so with one course of therapy, and the overall survival rate is superior to that achieved with standard therapy. Moreover, this new drug combination offers a significant advantage to patients who present with a high initial WBC.

That this study could be analyzed with a comparatively small number of patients on each arm is an advantage of the group sequential design. In contrast to the more commonly used analysis using a fixed sample size, the group sequential design allowed for formal interim analysis at specific accrual points during the course of the study. As shown in Table 2, the observed P value after 40 patients were entered on each arm, .006, was slightly higher than the nominal significance level required for closure of the study, which, at that point, was .004. However, at the subsequent accrual point of 60 patients per arm, the observed P value of .005 was less than the nominal P value of .019, and the study could therefore be closed.

In this study, we analyzed only newly diagnosed patients in an attempt to perform a balanced comparison of the two drug combinations. Recognizing that the disease itself is heterogenous with respect to morphology, clinical presentation, and nonrandom cytogenetic abnormalities, we nonetheless excluded only those patients with a documented myelodysplastic syndrome, secondary leukemia, or blastic phase of CML, subtypes of acute leukemia that have been shown to have a poor response to treatment with standard forms of therapy. The upper age limit of 60 was chosen in this trial because it was felt that the higher morbidity and mortality from infectious complications reported in older age patients might obscure the comparative antileukemia activity of the two drug combinations. It is recognized, however, that these are extremely important complications of the therapeutic approach to the treatment of this disease and as such cannot be ignored when considering a broader introduction of the drug into the overall population.

Preliminary results from two other randomized trials comparing IDR/Ara-C with DNR/Ara-C that have not restricted the upper age limit have been reported by Wiernik et al and Vogler et al. In the former study IDR was given at a dose of 13 mg/m² daily for 3 days, DNR at a dose 45 mg/m² daily for 3 days, and Ara-C at a dose of 100 mg/m² given as a continuous infusion daily for 7 days. Thirty-four of 51 evaluable patients (67%) achieved CR on the IDR/Ara-C arm compared to 27 of 51 patients (53%, P = .16) on the DNR/Ara-C arm. In the study reported by Vogler et al, the DNR dose and Ara-C doses were identical to those used by Wiernik et al but the IDR was slightly lower at 12 mg/m² daily for 3 days. Twenty-nine of 39 evaluable patients achieved remission (74%) on the IDR/Ara-C arm compared with 26 of 46 on the DNR/Ara-C arm (57%, P = .09). When patients under age 60 are analyzed in these two studies, the trend is still in favor of IDR/Ara-C, although the results are yet not statistically significant (Wiernik’s study: 81% v 65%, P < .1; Vogler’s study: 80% v 64%, P < .1).

The 58% remission incidence on the DNR/Ara-C arm of our study, while seemingly low, is actually within the range of previously reported adult trials in age groups under age 60. Rai et al first reported a 59% response incidence in this age group using the DNR/Ara-C dose and schedule that was subsequently incorporated by Wiernik et al and Vogler et al. Both Preisler et al and Yates et al, however, have reported higher incidences of response, 72% and 80% respectively, in similar age groups.

It is not clear whether higher doses of either DNR or Ara-C add substantially to remission incidence. Mayer et al increased the Ara-C dose to a total of 1,400 mg/m² (200 mg/m²/d given by continuous infusion daily for 7 days) while keeping the DNR dose at 45 mg/m² daily for 3 days and reported a 61% remission incidence in patients under age 59. Bishop et al recently reported a randomized trial using DNR/Ara-C (DNR 50 mg/m² daily for 3 days and Ara-C 100 mg/m² administered by continuous infusion daily for 7 days) with or without VP-16 and reported a 57% remission incidence in patients under age 55 on the DNR/Ara-C arm. It therefore seems reasonable to conclude that the remission incidence in patients within this age group is variable and reflects, most probably, the number of patients with good and poor risk features included in a particular study. As evidence continues to accumulate regarding the importance of specific cytogenetic abnormalities, efforts should be made to document the number of patients with each abnormality to determine
whether each study population is in fact a homogeneous group. Our groups were similar in cyto genetic distribution, although the number of patients with t(8;21) or inv(16) is small compared with other series.26,27

It is important to note, moreover, that criteria for defining complete remission and relapse differ among various studies. Many studies do not require two normal marrows within a specified time period to document remission40,50,51 and relapse has been defined in one previous study as a bone marrow that contained greater than 25% blasts.52 In the present study, if the criteria for documenting two remission bone marrows at least 1 month apart is removed, the remission incidence on the DNR/Ara-C arm increases to 66% and that on the IDR/Ara-C arm to 86%.

It should be noted that a greater proportion of patients on the DNR/Ara-C arm had a high WBC at presentation. However, an important finding in this study was that WBC alone did not affect response; rather, WBC combined with treatment proved important in determining response. Table 5 demonstrates this interaction, which shows the superiority of the IDR/Ara-C combination at high WBC's. Thus, while the imbalance in WBC appears to have depressed the response proportion in the DNR/Ara-C arm, the response on IDR/Ara-C arm is unaffected.

Variations in metabolic and pharmacologic properties of each anthracycline preparation may account for this finding. Both IDR and DNR undergo conversion to their respective alcohol metabolites, 13-hydroxyidarubicin (idarubicin-ol [IDR-ol]) and daunorubicin-ol (DNR-ol); however, unlike DNR-ol, IDR-ol has a prolonged plasma phase.12,13,16 Speth et al have shown that DNR-ol disappears from the plasma 144 hours after the third bolus dose, while IDR-ol remains at the initial steady state level 168 hours after the third bolus dose.13 Additionally, IDR-ol is as active as the parent compound in vitro against leukemic cell lines44 and purified IDR-ol has in vivo activity in murine leukemia models as well.25 IDR is a unique anthracycline analogue in this regard and the higher remission incidence on the IDR/Ara-C arm may reflect this pharmacologic advantage.

In this regard, it is important to note that the superior antileukemia activity of IDR/Ara-C is not associated with a more prolonged period of therapy-induced marrow aplasia (Table 3). Rather, the shorter recovery period for those patients who achieved a remission on the IDR/Ara-C arm is a function of the number of courses needed to achieve remission. If only those patients who achieved remission on one course of therapy are considered, the time to marrow recovery is approximately the same on each arm. Thus the IDR/Ara-C combination does not have a more suppressive effect on the normal marrow progenitor cell population, suggesting that the biologic efficacy of the drug is at the level of the leukemic cell.

Postconsolidation questions were more difficult to address on these two sequential studies. Too few patients were randomized on the L-19 Protocol to observation alone versus maintenance therapy with low dose Ara-C and no conclusion could be made regarding the contribution of the latter form of treatment to overall survival. Similarly, only a small fraction of eligible patients received either an allogeneic or autologous bone marrow transplant on the L-22 Protocol (Table 7). Such low patient accrual is in accordance with other previous reports that suggest that marrow transplantation, which may offer a survival advantage, is available to only a small proportion of the adult AML population.53,54 Nonetheless, overall survival for the 120 evaluable patients on this study shows an advantage for those patients who received IDR/Ara-C regardless of postinduction therapy (Fig 3). Included in these curves are the 13 patients (five on the L-19 Protocol and eight on the L-22 Protocol) who underwent transplantation after induction and consolidation therapy. As Table 6 demonstrates, treatment arm, age, and favorable cytogenetics were all important factors for survival; these three variables have all been previously documented to be significant in this regard.25,26,47

Nonhematologic toxicity was equivalent on both arms of study. Particularly important is the finding that a small but equal number of patients had a significant (>10%) absolute decrease in their LVEF after consolidation therapy. This would suggest that both drugs had a equivalent cardiotoxic effect that would not have been predicted by the preclinical data in animal models.49

In summary, we suggest that IDR offers a distinct advantage over DNR for remission induction in adult AML. The difference in pharmacologic properties between the two anthracycline preparations may well play an important role. However, confirmatory studies in older patients will be necessary to unequivocally define its role in the treatment of this disease.

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Results of a randomized trial comparing idarubicin and cytosine arabinoside with daunorubicin and cytosine arabinoside in adult patients with newly diagnosed acute myelogenous leukemia

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