High-Dose Cytarabine and Daunorubicin Induction and Postremission Chemotherapy for the Treatment of Acute Myelogenous Leukemia in Adults


Seventy consecutive adult patients with acute myelogenous leukemia (AML), median age 44 years, received high-dose cytarabine (3 g/m² every 12 hours for 12 doses) followed by daunorubicin (45 mg/m² daily for three doses) for remission induction. A single, identical course was planned for postremission therapy. Complete remission (CR) was achieved in 63 patients (90%, 95% confidence interval [CI] 83% to 97%), 60 after a single course. Eight patients were selected to undergo elective bone marrow transplantation (BMT) during first CR. Of the remaining 55 patients, 40 (73%) underwent planned post-CR therapy; 15 patients did not, owing to early relapse, excessive toxicity from the induction chemotherapy, or refusal. Nineteen patients, including 13 who received planned post-CR therapy, remain in continuous CR at a median follow-up of 5.2 years (range 3.0 to 7.1 years). The 5-year actuarial leukemia-free survival was 30% (95% CI, 19% to 42%) for all patients achieving CR and 32% (95% CI, 19% to 47%) for the 40 patients who received the planned post-CR chemotherapy. Analysis of various putative prognostic factors for CR and overall and leukemia-free survival showed significance for a previous history of myelodysplasia, higher initial leukocyte counts, certain French-American-British (FAB) types, and certain abnormal karyotypes. None of these factors was consistently significant regarding the above parameters, although small patient numbers in certain analyses may have obscured significant associations. Myelosuppression was occasionally prolonged after remission induction and especially post-CR therapy. Severe cerebellar toxicity was observed in 13 patients; in 11 cases, this toxicity was fully reversible. Other serious complications were infrequent. Intensive chemotherapy with high-dose cytarabine and daunorubicin has substantial antileukemic activity in adult AML, and may represent an improvement over conventional therapy. Relapses were common, however, even in patients who received planned therapy, and substantial toxicity was observed. The optimum use of this regimen in AML remains to be determined.

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during this entire period. Eligibility criteria were as follows: (1) unequivocal diagnosis of AML by morphologic and cytochemical criteria; (2) age 15–60 years; (3) no previous intensive therapy (single-agent therapy, usually hydroxyurea, was permitted); (4) absence of severe, nonleukemic organ dysfunction; and (5) informed consent. This study was performed under the auspices of institutional review board approval at each institution.

**Patient Characteristics**

Pretreatment patient characteristics are shown in Table 1. Only 17% of patients were aged less than 25 years; 46% were aged 45–60 years. Seven patients had an antecedent myelodysplastic syndrome, and one patient developed AML after adjuvant chemotherapy for breast cancer. All but two patients had AML criteria; (2) age 15-60 years; (3) no previous intensive therapy (single-agent therapy, usually hydroxyurea, was permitted); (4) absence of severe, nonleukemic organ dysfunction; and (5) informed consent. This study was performed under the auspices of institutional review board approval at each institution.

**Chemotherapy**

**Drug administration.** Patients received chemotherapy in doses calculated by actual or ideal body weight (less), using cytarabine 3.0 g/m² by 1-hour intravenous (IV) infusion every 12 hours for 12 doses (days +1 through +6, inclusive), followed by daunorubicin 45 mg/m² by rapid IV infusion daily for three doses (days +7 through +9, inclusive) (Fig 1). Drug doses were not adjusted in patients with abnormalities of renal or hepatic function. This regimen was administered to all patients at these doses, except when cerebellar toxicity was observed. In such cases, cytarabine was promptly discontinued but daunorubicin was administered as planned.

**Remission induction.** A repeat bone marrow (BM) biopsy was performed on day +15; patients who achieved hypoplasia with ≤5% leukemic cells underwent another biopsy at day +30. Patients with residual AML at either day +15 or +30 were to receive an identical reinduction course unless the level of response was deemed minimal; for such cases, further therapy was individualized. For patients in whom the level of response was unclear, BM biopsies were repeated weekly until remission status was clarified. A similar evaluation was performed if reinduction therapy was required.

**Post-CR therapy.** Patients in CR after remission induction therapy who were aged ≤45 years and had histocompatible sibling donors were offered elective allogeneic BM transplants (BMT). All others were scheduled to receive another single, identical course of chemotherapy as soon as CR was documented, all toxicities of the induction therapy had resolved, and a hospital bed was available.

**Supportive Care**

Patients were nursed in single rooms using conventional reverse-isolation techniques and high-efficacy particulate-air (HEPA) filtration. Indwelling central venous catheters, allopurinol and vigorous IV hydration, corticosteroid eye drops, and antiemetic precautions were used routinely. Platelet (pooled or HLA matched, if required) and erythrocyte transfusions, IV antimicrobials, Amphotericin B and IV hyperalimentation were used as indicated.

**Definitions**

CR was defined by standard criteria. Patients who died with any evidence of AML were considered to have died of leukemia, regardless of the proximate cause of death. Cytogenetics were classified as follows: (a) normal, ie, diploid; (b) abnormal but favorable, ie, t(8;21), t(15;17), or abnormalities of 16q22; (c) abnormal and unfavorable, ie, trisomy 8, t(9;22), deletion of all or part of chromosomes 5 and/or 7, abnormalities of chromosome 11, and complex abnormalities; (d) abnormal, all others; and (e) inadequate cytogenetics.

**Analyses**

Endpoints considered in the data analysis were as follows: (a) CR; (b) overall survival (calculated from the first day of chemotherapy until death or end of follow-up); censored observations occurred only at the end of follow-up; (c) leukemia-free survival (calculated from the first day of CR to relapse, death, or the end of follow-up); censored observations occurred only at the end of follow-up without relapse); and (d) cumulative incidence of relapse (calculated from the first day of CR to relapse, death, or end of follow-up; censored observations occurred only at death of nonleukemic causes or the end of follow-up without relapse). For this analysis, follow-up ended August 31, 1990; minimum follow-up is 3 years.
Various factors were evaluated for prognostic significance, including age, sex, antecedent myelodysplasia, leukocyte count at diagnosis, FAB subtype, and karyotype; age and leukocyte count were analyzed as continuous variables. Age was also analyzed as a categorical variable for comparison with our previous report. Leukemia-free and overall survival and cumulative relapse were estimated by the Kaplan-Meier method. CIs were calculated using Greenwood's estimate of the variance of the transformed Kaplan-Meier statistic. Leukemia-free and overall survival curves were computed for prognostic groups within the total sample. Statistical tests of comparison were made with the log-rank test for categorical variables and the likelihood ratio test using the Cox proportional hazards model for continuous variables. Multivariate analysis was performed with the Cox proportional hazards analysis.

RESULTS

Remission Induction

All but 5 patients who developed cerebellar toxicity during therapy received prescribed doses of both cytarabine and daunorubicin as remission induction; in these patients, one to three doses (median two) of cytarabine were omitted. Of the entire group of 70 patients, 63 (90%, 95% CI, 83% to 97%) achieved an initial CR, including 60 after a single cycle, at a median of 35 days (range 21 to 80 days) after initiation of induction chemotherapy. Both the presence of antecedent myelodysplasia and higher leukocyte counts at diagnosis were associated with a decreased probability of achieving CR (P = .003 and .04, respectively). After inclusion of these two factors, proportional hazards analysis showed no other significant factors.

Of the 10 patients who did not achieve CR after the first induction cycle, six did not receive reinduction therapy owing to early death (fatal leukostatic complications after receiving only a single dose of cytarabine in one patient and pancytopenic complications in four others) or a minimal response (in one patient). Of the remaining four patients who received a reinduction cycle, three entered CR. One of these patients, with acute promyelocytic leukemia, had been judged a failure on day +15 and treated, but reinduction therapy was abruptly terminated as her blood counts recovered while she was receiving this therapy. Although CR may have been achieved without further therapy, this patient was coded as requiring reinduction to achieve CR.

Overall Survival in All Patients

Twenty-two patients remain alive in CR, including three patients in second CR (two after BMT), with a median follow-up of 5.6 years (range 3.1 to 7.2 years). As shown in Fig 2, the 5-year actuarial overall survival in all 70 patients is 31% (95% CI, 20% to 42%). A history of previous myelodysplastic syndrome was significantly (P = .04) correlated with decreased overall survival. The abnormal karyotype classifications of "unfavorable" and "other" were also of borderline significance (P = .06). Only younger age (P = .02) correlated with improved survival according to the proportional hazards analysis. Causes of death are shown in Table 2.

Analysis of All Patients Who Achieved CR

As shown in Fig 3A, 19 of these 63 patients remain in continuous CR with a median follow-up of 5.4 years (range 3.0 to 7.1 years), a 5-year leukemia-free survival of 30% (95% CI, 19% to 42%). Karyotype was the only variable significant for leukemia-free survival (P = .02); of the 13 patients with abnormal karyotypes classified as "unfavorable" or "other," only one is in continuous CR. No other variables were significant in the proportional hazards analysis after correction for karyotype.

Thirty-eight of the 63 patients who attained CR eventually relapsed. Most relapses (92%) occurred during the first 2 years; the latest relapse occurred at 3.5 years. The 5-year cumulative incidence of relapse in all CR patients is 65% (95% CI, 52% to 77%). Abnormal karyotype (as detailed above) and FAB subtype (the subgroups of AML M5, M6, and M7 fared poorly) were correlated with a higher cumulative incidence of relapse (P = .009 and .08, respectively). No other factors were significant in the proportional hazards analysis after correction for karyotype.

Patients who received planned post-CR therapy. Forty patients received a single post-CR cycle according to protocol. Thirty-four of these patients received prescribed doses of cytarabine and daunorubicin; in the six who

<table>
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<tr>
<th>Table 2. Causes of Death</th>
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<tr>
<td>Cause</td>
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<tr>
<td>Leukemia</td>
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<tr>
<td>Hyperleukocytosis*</td>
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<tr>
<td>Primary resistance</td>
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<tr>
<td>Relapse</td>
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<tr>
<td>Pancytopenia with marrow aplasia</td>
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<td>After induction</td>
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<td>After consolidation</td>
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<tr>
<td>Complications of BMT</td>
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<tr>
<td>Performed in first CR</td>
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<tr>
<td>Performed in other status</td>
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<tr>
<td>Total</td>
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Abbreviations: BMT, bone marrow transplantation; CR, complete remission.

*Died after first dose of cytarabine.
developed cerebellar toxicity, one to three (median two) doses of cytarabine were deleted. The median time from the achievement of CR to the first day of protocol post-CR therapy in these 40 patients was 27 days (range 0 to 176 days).

Thirteen of these patients are alive and in continuous CR; none have symptoms (except for one patient who developed metastases from breast cancer) at a median follow-up of 5.4 years (range 3.0 to 7.1 years). As shown in Fig 3B, the 5-year leukemia-free survival in these patients is 32% (95% CI, 19% to 47%). No variable was significantly related to leukemia-free survival, although the abnormal karyotypes classified as “unfavorable” or “other” exhibited a trend toward significance ($P = .07$).

In those 40 patients who received both induction and protocol post-CR cycles, the cumulative incidence of relapse is 62% (95% CI, 47% to 78%); again, most relapses (91%) occurred in the first 2 years after patients achieved CR, although the latest relapse occurred at 3.5 years. Higher initial leukocyte counts ($P = .03$) and the karyotype abnormalities already described ($P = .05$) were associated with an increased likelihood of relapse. After correction for initial leukocyte count, no other variables were significant in the proportional hazards analysis.

**Patients who received elective BMT.** Eight patients were scheduled for elective BMT in the initial CR; one of these patients was found to be in an unsuspected (“early”) relapse at that time. Transplants were performed a median of 2.5 months (range 2 to 5 months) after patients began therapy. Of these eight patients, seven received allogeneic bone marrow transplants; four remain in continuous CR at 5.3, 4.9, 4.7, and 4.1 years from transplantation, two relapsed, and one died of complications. One patient with morphologic CR but persistent karyotypic abnormalities (and no suitable donor), after three courses of high-dose cytarabine and daunorubicin chemotherapy, received busulfan, cyclophosphamide, and an autologous BM reinfusion treated ex vivo with 4-hydroperoxycyclophosphamide (4-HC)$^3$ and remains well 3.2 years later.

**Remainder patients.** In the 15 patients who entered CR but did not receive an elective BMT, protocol post-CR therapy was precluded for the following reasons: cerebellar toxicity ($n = 5$), early relapse ($n = 4$), refusal of any further therapy ($n = 3$), exacerbation of severe chronic depression ($n = 1$), and *Aspergillus* sp pneumonia ($n = 1$). Only one of these patients is alive; this patient received two further courses of conventional-dose cytarabine and amsacrine therapy after having severe cerebellar toxicity and remains in continuous CR 5.5 years later.

**Relapses**

Most relapses were medullary; there were no obvious isolated CNS relapses, although patients were not specifically reevaluated for meningeal leukemia in the absence of symptoms. Four relapses occurred before post-CR therapy could be given, three occurred in the nine patients who received elective BMT, 22 occurred in the group of 40 patients who received protocol consolidation, six occurred in the patients who received other post-CR therapies, and three occurred in the patients who refused post-CR therapy.

**Salvage chemotherapy.** Relapses were managed off protocol. Of the 22 patients who relapsed after both planned induction and post-CR therapy, however, seven were retreated with regimens containing high-dose cytarabine in an identical dose and schedule, combined with conventional doses of either mitoxantrone ($n = 5$), amsacrine ($n = 1$), or daunorubicin plus etoposide ($n = 1$). All but one achieved second CR, but only one of these patients remains in a continuous second CR of 3.2 years (after a first CR of 1.3 years).

**Salvage BMT.** Ten patients underwent BMT in nonelective situations. Allogeneic BM was used in five, and autologous BM (harvested during CR and treated ex vivo with 4-HC) in five. Two patients in the former group remain alive in second CR at 5.8 and 4.7 years after transplantation.

**Toxicity**

**Hematologic toxicity.** Nine patients died of pancytopenic complications, four after induction therapy (at days +14, +14, +38, and +58) and five after protocol post-CR therapy (at days +18, +31, +38, +53, and +115). In patients who survived, the recovery kinetics of neutrophils (absolute neutrophil count [ANC] ≥ 0.5 × 10⁹/L) and platelets (the last day of platelet transfusion) were as shown in

<table>
<thead>
<tr>
<th>Cycle</th>
<th>No. of Patients</th>
<th>Day ANC* &gt; 0.5 × 10⁹/L</th>
<th>Day of Last Platelet Transfusion†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction (first)</td>
<td>62†</td>
<td>26 (19-40)</td>
<td>27 (12-48)</td>
</tr>
<tr>
<td>Induction (second)</td>
<td>5</td>
<td>30 (27-38)</td>
<td>26 (21-51)</td>
</tr>
<tr>
<td>Post-CR</td>
<td>40</td>
<td>31 (21-54)</td>
<td>36 (13-114)</td>
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*Absolute neutrophil count = neutrophils + bands.
†Usually an unsupported level of approximately 20.0 × 10⁹/L on this day.
‡Includes four partial responders.
§Median (range) days from initiation of therapy.
Table 3; count recovery from the post-CR course was prolonged by approximately 1 week as compared with the induction course.

Nonhematologic toxicity. Serious nonhematologic toxicity was limited to the cerebellum; obvious cerebral toxicity was not observed. Thirteen cases (11%) of cerebellar toxicity were observed in all 116 courses: five (7.1%) in the 70 patients who received one course, eight (18.2%) in the 44 patients who received two courses in close succession, and none in the single patient who received three courses. None of the 7 patients who received other high-dose cytarabine regimens as salvage chemotherapy after relapse developed cerebellar toxicity. In addition, none of the four patients who developed cerebellar toxicity and subsequently received cytarabine (100 to 200 mg/m² by continuous infusion for 5 to 7 days) developed recurrent cerebellar toxicity. None of these latter patients received high-dose cytarabine again, however. In two patients, cerebellar toxicity was not completely reversible; however, both patients slowly regained most neurologic function. There was no obvious correlation between abnormal renal function and cerebellar toxicity (data not shown).

Because a previous analysis had indicated that age ≥ 50 years was the major risk factor for cerebellar toxicity, we also analyzed the variable of patient age categorically (ie, <50; 50 years); the incidence of cerebellar toxicity was 8 of 84 courses (10%) v 5 of 32 courses (16%), respectively (P = .55). Of the eight patients aged <50 years who developed cerebellar toxicity, three were in their 20s and all others were aged 44 to 49 years.

DISCUSSION

Resistance to chemotherapy is assumed to be the chief cause of failure in AML, and a number of approaches have been used to circumvent this problem; for example, rotating exposure to regimens with differing mechanisms of cytotoxicity has been used. Although theoretically of interest, this approach is hindered by the lack of a number of proven non-cross-resistant regimens. We therefore used two of the most active agents in AML to the anticipated limits of tolerance for induction and a single post-CR cycle. We also tried to administer these two courses as rapidly as possible, another tactic designed to reduce drug resistance.

High-dose cytarabine and daunorubicin as used in this study has substantial antileukemic activity, as indicated by the CR rate of 90% (usually after a single cycle) in adult patients selected only by age ≤ 60 years in a multiinstitutional study. This CR rate appears to be in excess of the 60% to 70% usually obtained in adult AML patients who receive less intensive induction with these same agents or with high-dose cytarabine alone as used in this schedule; however, this point must be regarded as tentative without additional supporting data. Although CR in itself is an inadequate therapeutic goal in AML, it is presumed to be a necessary condition for cure. Because most leukemic cell kill probably occurs during the first few cycles of chemotherapy, a more potent induction regimen may also increase duration of CR, or even the percentage of patients cured, in patients who would have entered CR with less intensive induction. Unfortunately, the design of this study precluded a precise evaluation of this point. An induction regimen that produced a higher CR rate even without a higher median cell kill would also be of benefit, provided that effective post-CR therapy could be used in these patients. Again, whether this goal was achieved is unclear; a 30% durable CR rate in the 90% of patients achieving CR would represent an improvement over conventional regimens with a similar durable CR rate in a lower percentage of patients. Therefore, the efficacy of this regimen as compared with more conventional regimens is relevant, both intrinsically as well as in regard to the experience comparing conventional AML therapy with myeloablative therapy and allogeneic BMT. Specifically, because a recent update of a Seattle study suggests the superiority of the latter approach for a subset of AML patients, and because that study was performed using chemotherapeutic regimens containing cytarabine in conventional doses, an improved antileukemic effect with high-dose cytarabine regimens might produce results closer to those obtained with BMT. The present study was not designed to answer this important question, however, and conclusions would be speculative. Similarly, neither has the question of the relative efficacy of this as compared with other high-dose cytarabine regimens been addressed directly. To answer these questions definitively, prospective randomized trials would be required.

Because this study was designed to improve on our previous experience, it is important to compare these studies, despite their intrinsic differences. Specifically, while no treatment group in the current study is comparable to the patients in the previous study, we were unable to demonstrate obvious superiority of the current approach. There are several possible explanations for this result. First, two courses given as induction and post-CR therapy may be no more effective than a single course of high-dose cytarabine and daunorubicin given after a CR achieved with more conventional therapy. Second, results of the current study may merely reflect the intrinsic activity of this regimen in a different, possibly less selected patient population. The latter point may be important; in our previous study, we did not evaluate certain prognostic factors (eg, previous history of myelodysplasia, initial leukocyte count, cytogenetics) identified in this study as unfavorable; perhaps fewer patients in that series had these features. In this regard, a more obvious difference between the studies was the failure of the current study to reproduce the excellent results in patients aged ≤ 25 years. Although younger age was correlated with improved overall survival, it was not significantly associated with improved leukemia-free survival either in the entire group of CR patients or only in those patients who received protocol post-CR therapy (analyzing age either as a continuous variable or as a categorical variable as before). Finally, because the current study used an induction regimen that may produce a higher CR rate than did the conventional-dose cytarabine regimens used in the previous study, we may speculate that if more patients had been induced into CR by the more intensive regimen, this enlarged group might have contained a number of patients
with a relatively resistant form of AML destined to relapse. Insufficient information exists to favor any of these possible explanations; some or all may be involved.

We also observed that use of high-dose cytarabine and daunorubicin in this manner produced profound hematologic and nonhematologic toxicity. The hematologic toxicity may be intrinsic to the high CR rate, but prolonged pancytopenia (ANC < 0.5 x 10^9/L ≥ 30 days) was fatal in six patients; moreover, prolonged pancytopenia prevented or at least delayed further therapy in some cases. Similarly, cerebellar toxicity compromised further high-dose cytarabine therapy in some patients, although most of these patients subsequently received other therapies (including cytarabine in more conventional doses) without excessive toxicity. Overall toxicity, a description that includes patients with the above problems as well as those patients who refused further therapy without a medical cause, precluded planned therapy in 25% of patients. This appears to be a higher percentage than has been observed in more conventional regimens.

Finally, our analysis of prognostic factors yielded few surprises; patients with previous histories of myelodysplasia, higher initial leukocyte counts, as well as certain previously recognized FAB types and cyogenetic abnormalities, had inferior outcomes. None of these factors was associated with poor results in all analyses, however, an observation that may be explained by relatively small patient numbers in certain categories. Moreover, although the usual suggestion is to use more potent therapies (such as allogeneic BMT) in such patients, it is likely that the patients will do poorly with those therapies as well. Therefore, although subsequent efforts will be directed at reducing both toxicities and relapses, methods by which this will be achieved are not clear, as conventional-dose regimens are associated with lower toxicity but high failure rates, and regimens of even greater intensity (ie, those using BM support) are associated with greater toxicity. In lieu of the appearance of unique new agents, these considerations suggest that the limits of chemotherapy have been reached, and new approaches are required.

NOTE ADDED IN PROOF

As of February 1, 1991, the status of all 19 surviving patients was unchanged. The median leukemia-free survival in these patients is 5.6 years (range 3.4 to 7.5 years).

ACKNOWLEDGMENT

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