REVIEW ARTICLE

A Critical Appraisal of Low-Dose Cytosine Arabinoside in Patients With Acute Non-Lymphocytic Leukemia and Myelodysplastic Syndromes

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We reviewed 53 publications reporting 751 patients with hematologic malignancies treated with low doses (5 to 20 mg/m²/d) of cytosine arabinoside (LoDAC). Of 507 patients evaluable for response, complete remission (CR) rates varied from 32% for patients with primary acute non-lymphoblastic leukemia (1°ANLL) to 16% for patients with hematologic malignancies secondary to previous chemotherapy or following a myelodysplastic syndrome (MDS) (2°ANLL), and 16% for MDS. Median duration of CR was 9.5 months for 1°ANLL, and 10.5 months for both 2°ANLL and MDS. Based on limited available survival data, overall median survival for these groups was 9 months, 3 months, and 15 months, respectively. Only three CRs were reported of 31 evaluable patients treated for a variety of other hematologic malignancies. CR rates for patients with 1°ANLL ≥ 50 years old was 56%, compared with 29% < 50 years old (P = .10). While prior chemotherapy was more common in 1°ANLL patients < 50 years of age (86% v 21%; P < .001), it did not influence response rates in those > 50 years of age, suggesting other biases. Hematologic toxicity was mentioned in only 33 of 53 publications, affecting 254 of 289 patients (88%), with at least 15% treatment-related deaths. LoDAC hypothetically acts as a differentiating agent; however, correlative laboratory studies were rarely performed. Cytogenetic data were available for only 15%, and in vitro studies for 10% of all patients with marked discrepancies in the interpretation of results. LoDAC is clearly cytotoxic for both malignant and normal hematopoietic cells. While large numbers of patients have been reported, the lack of well-designed clinical trials prohibits definitive conclusions as to its role as a differentiating agent. Future LoDAC studies should determine optimal dose and schedule, with clinical laboratory correlates to assess differentiation. Trials in ANLL comparing LoDAC with conventional chemotherapy, and in MDS with supportive care alone, may help identify the role of LoDAC. Until appropriate indications can be identified, LoDAC should not be routinely used in clinical practice.

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OVER THE PAST DECADE, a number of observations have been used to support the use of low doses of cytosine arabinoside (LoDAC) (5 to 20 mg/m²/d) in the treatment of patients with acute non-lymphoblastic leukemia (ANLL) and myelodysplastic syndromes (MDS). First, cytosine arabinoside (ara-C) at conventional doses (100 to 200 mg/m²/d for five to ten days) or high doses (3 gm/m² every 12 hours for six to 12 doses) is the most active chemotherapy agent for the treatment of patients with ANLL.[1-4] Second, both ANLL and MDS are presumed disorders of cellular maturation,[5,6] and low levels of ara-C are capable in vitro of inducing the histologic and functional differentiation of HL-60 cells, a human acute promyelocytic leukemia cell line.[7] Third, since conventional-dose ara-C has predictable and tolerable toxicity, LoDAC should be associated with even less toxicity, possibly improving the therapeutic index. Fourth, LoDAC can be administered subcutaneously, permitting outpatient treatment. Finally, a number of preliminary reports suggested clinical efficacy for LoDAC and this treatment has been increasingly used for patients with MDS and elderly patients with ANLL.

The initial description by Baccarani and Tura in 1979 of the use of LoDAC in patients with ANLL[8] and Wisch et al in MDS[9] have been followed by numerous publications. Nevertheless, despite a large number of reports, the use of LoDAC remains extremely controversial. In an attempt to clarify the role of LoDAC in ANLL and MDS, we reviewed the available data since 1979 and estimated response rates, survival, tox-

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icity, and evidence for LoDAC as a differentiating agent in human ANLL and MDS. This report presents the results of this analysis.

METHODS

Identification of Reports

The English literature since 1979 was searched using the Cancerline data base. Other sources included all of the publications cited in the bibliography of each report, Current Contents (Institute for Scientific Information, Philadelphia), and the Proceedings of the American Society of Hematology, American Society of Clinical Oncology, American Association for Cancer Research, and the American Federation for Clinical Research. These publications included refereed journal articles, meeting abstracts, and letters to journals.

Patient Selection

Patients were considered eligible for the current analysis only if they were diagnosed as having a hematologic malignancy and were treated with 5 to 25 mg/m^2/d of ara-C. Reports were carefully analyzed so that patients who appeared in multiple publications were included only once in the data.

When a diagnosis was presented without objective supporting data, it was included in the current analysis as reported by the original investigators. If objective data were provided, they were analyzed, and when indicated, diagnoses were reclassified according to the French-American-British (FAB) classification.[10,11]

Response Criteria

We defined a complete response (CR) as consisting of the following: WBC count of $\geq$ 3,000/μL with a normal differential, platelet count of $\geq$ 100,000/μL, a bone marrow that is normocellular or only moderately hypocellular with $<$ 5% blasts, no myelodysplasia, and where applicable, reversion to a normal karyotype. An acceptable definition of partial response (PR) included any one of the following: (1) normalization of all three peripheral blood counts with a bone marrow revealing either myelodysplasia, persistence of an abnormal karyotype, marked hypocellularity, or a percent of blasts that was substantially less than the initial marrow sample but which remained $\geq$ 5%; or (2) normalization of peripheral blood counts despite a persistence of 1% to 5% blasts in the differential count. Clinical states other than a CR or PR were classified as no response (NR). When CR or PR was claimed but not defined, the patient was classified according to the investigators' designation, but when a response as presented failed to satisfy the above criteria, it was reclassified accordingly.

Similarly, assessment of toxicity was based on reporting by the original investigators. Notation of myelotoxicity was accepted with or without supporting laboratory values. Drug-related deaths were recorded when stated by the investigator or inferred from the data presented.

The original investigators of two publications were contacted for minor clarification of the responses of individual patients (K. Miller, M. Beran, personal communication, October 1985), when limited information was needed to substantially increase the number of evaluable patients in the series.

Standard methods of statistical analysis were used: contingency chi-square tests with continuity corrections and Kaplan-Meier product-limit estimators of the distribution of survival and CR duration. All significance levels were of the two-sided type.

RESULTS

Patients

Fifty-three reports from the English literature published between January 1, 1979 and December 31, 1985 were identified;[9,12–63] including 751 patients. Of these, 30 were refereed publications accounting for 516 patients, 16 were abstracts accounting for 198 patients, and seven were letters to journals which accounted for the remaining 37 patients. The number of cases in each publication ranged from one to 160, with a mean of 14 and a median of 9. At least six refereed publications were preceded by abstracts or letters, and only the final publication was included in the total number of reports. Only data from the final report were included in the analysis.

Patient age was available for 224 cases, and ranged from 11 to 89 years with a median of 65 years. Of the 751 total patients, 581 were reported as either primary ANLL (1°ANLL) or MDS (77.4%). Of 88 patients with secondary hematologic malignancies (2°ANLL), six had 2°MDS, the other 82 having 2°ANLL. Therefore, these two groups of patients with secondary malignancies were grouped together for analyses. The remaining patients were diagnosed as chronic myelogenous leukemia in blast crisis (n = 18), chronic myelogenous leukemia (n = 3), acute lymphocytic leukemia (n = 12), non-Hodgkin's lymphoma (n = 4, three of which were in a leukemic phase), chronic lymphocytic leukemia (n = 7), acute undifferentiated leukemia (n = 2), or a poorly defined myeloproliferative disorder (n = 1) (Table 1). No diagnosis was provided for the remaining 35 patients (4.8%).

Response to Therapy

Of the 751 patients, 507 (68%) were evaluable for response (Table 2). Reasons for inevaluability were most often failure to identify responses by individual patient, insufficient data to characterize the response, the use of concurrent cytotoxic chemotherapy, patients designated as "inevaluable" by the original investigators, unspecified dose or schedule, or a combination of these features.

Table 2 lists the frequency of responses report-

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Table 1. Clinical Diagnosis of 751 Patients Treated With LoDAC

Diagnosis	Total Patients (%)
1° ANLL	340 (45)
Primary MDS	241 (32)
RA	11 (2)
RAEB	51 (7)
RAEB-T	41 (6)
CMML	16 (2)
Not specified	101 (13)
Secondary disorders	88 (12)
ANLL	82 (11)
MDS	6 (< 1)
Other	47 (6)
CML-BC	18 (3)
CML	3 (< 1)
ALL	12 (2)
AUL	2 (< 1)
NHL	4 (< 1)
CLL	7 (1)
Myeloproliferative disorder	1 (< 1)
Not stated	35 (5)
Total	751

Abbreviations: 1° ANLL, primary acute non-lymphocytic leukemia; MDS, myelodysplastic syndrome; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RAEB-T, RAEB in transformation; CMML, chronic myelomonocytic leukemia; CML-BC, CML in blast crisis; CML, chronic myelogenous leukemia; ALL, acute lymphocytic leukemia; AUL, acute undifferentiated leukemia; NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia.

ed for the 507 evaluable patients. Patients were divided into four groups: (1) primary, or de novo, ANLL (1°ANLL) (n = 237); (2) 2°ANLL, which included ANLL developing after a prior history of MDS, or ANLL or MDS subsequent to chemotherapy for another malignancy (n = 69), (3) MDS (n = 170); and (4) a group of miscellaneous hematologic malignancies (n = 31) (Table 2). Thirty-two percent of patients with 1°ANLL achieved a CR following treatment with LoDAC, a significantly better response rate than reported for patients with 2°ANLL (16%; $P < .025$) or MDS (16%; $P < .005$). Although chronic myelomonocytic leukemia appeared to have a higher rate of CR than the other MDS (35% *v* 15%), the number of evaluable patients with chronic myelomonocytic leukemia was too small (n = 17) to draw any conclusions. Therefore, this subset of MDS patients was included as part of MDS for further analyses. Only three CRs were noted of 31 evaluable patients in the miscellaneous group.

There is a theoretic pharmacologic advantage for the induction of cellular differentiation using continuous administration of LoDAC as compared with intermittent schedules.[64,65] Therefore, we compared the results reported with these two schedules in which such data were available. For patients with 1°ANLL, the CR rate for 11 patients who received LoDAC by continuous infusion was 64% compared with 34% for the 195 patients treated with intermittent doses. For patients with MDS, the CR rate for the 15 patients who received a continuous schedule was 20% compared with 16% for the intermittent schedules. Although there is some suggestion of superiority for continuous infusion schedules for patients with 1°ANLL, these data are obviously difficult to interpret since they are limited and since there have been no direct comparisons of the two schedules.

We next examined the data to determine any clinical factors that may have influenced response. CR rate for patients with 1°ANLL ≥ 50 years of age was greater than for patients < 50 years of age (56% compared with 29%), although this difference was not statistically significant ($P = .10$). Since younger patients are more likely to be treated aggressively, a lower response rate to LoDAC might be expected as the

Table 2. Response Rates for LoDAC-Treated Patients Analyzed by Diagnosis

Diagnosis	No. of Responding Patients (%)*			
	No. of Patients	CR	PR	NR
Primary ANLL	237 (48)	77 (32)	31 (13)	129 (54)
MDS	170 (34)	27 (16)	36 (21)	107 (63)
Secondary ANLL/MDS	69 (14)	11 (16)	10 (14)	48 (70)
Other	31 (6)	3 (10)	13 (42)	15 (48)

Abbreviations: CR, complete remission; PR, partial remission; NR, no response.
*Numbers based on 507 patients evaluable for response.

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result of prior therapy. Where prior therapy data were available, prior chemotherapy for ANLL was more common for younger patients (12 of 14, 86%) than older patients (13 of 61, 21%; $P <$ .001). Of the older patients who had been previously treated, 54% achieved a CR compared with 48% of previously untreated patients. For the younger patients, CR rates for the previously treated and untreated groups were two of two and two of 12, respectively. Therefore, it would appear that other selection biases may account for the difference in response rates between the age groups.

When similar analyses were performed for patients with MDS, CR rates for the two age groups were similar: 6% and 17%, respectively, for those under 50 years and for the older age group. The influence of prior therapy for MDS could not be assessed since only three patients $\geq$ 50 years and one patient $<$ 50 years had received previous chemotherapy for MDS.

Response duration and overall survival for the patient groups were also examined. Duration of remission was available for 85 of the 118 patients (72%) recorded as having achieved a CR. Median duration of CR for 1°ANLL, 2°ANLL, and MDS were 9.5 months, 10.5 months, and 10.5 months, respectively (Fig 1). Survival information was available only for 74 patients, and the median survival for each group as a whole was 9 months, 3 months, and 15 months, respectively (Fig 2). We also examined survival by response, in spite of the difficulty in interpreting such data,[66] and found little evidence that achieving a CR exerted a substantial influence on survival.

Since one of the potential advantages of LoDAC therapy is reduced drug-related toxicity, we next tabulated the side effects that were reported. Other than myelotoxicity, few drug-related toxicities were reported. However, drug-induced hematologic toxicity was mentioned in only 33 of the 53 reports containing 374 cases (50%). Myelotoxicity was noted in 254 of the 289 patients (88%) for whom the investigators presented data describing drug-related toxicities. Deaths were considered to be the result of treatment in 15% of those reported to exhibit myelotoxicity.

DISCUSSION

Despite the large numbers of patients treated with LoDAC for hematologic malignancies, the role of this therapy is at best controversial. For example, although the aggregate CR rate for patients with 1°ANLL was 32%, there is considerable variability among reports. In 15 published series, each of which contained at least eight patients with ANLL, four reported CR rates of $\geq$ 50%, while eight reported CR rates of $\leq$ 18%. To a large extent, this reflects the small sample size in each publication. Some investigators state that LoDAC is extremely well tolerated, yet myelotoxicity that was often severe was noted in 88% of those patients for whom data were available, and 15% of those died as the result of treatment.

There are a number of reasons why LoDAC remains in an ambiguous position. First, while it has differentiating activity in vitro, few attempts have been made to assess its role as a differentiating agent in clinical trials. More than a decade ago, Greenberg et al[5] and Golde and Cline[6] postulated that acute leukemia and "pre-leukemia" were disorders of impaired cellular maturation.

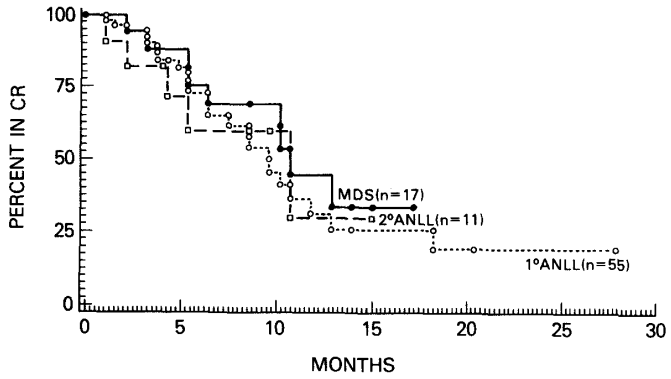

Fig 1. Kaplan-Meier estimates for the median duration of CR for 85 patients with 1°ANLL (open circles), 2°ANLL (open squares), and MDS (solid circles) treated with LoDAC.

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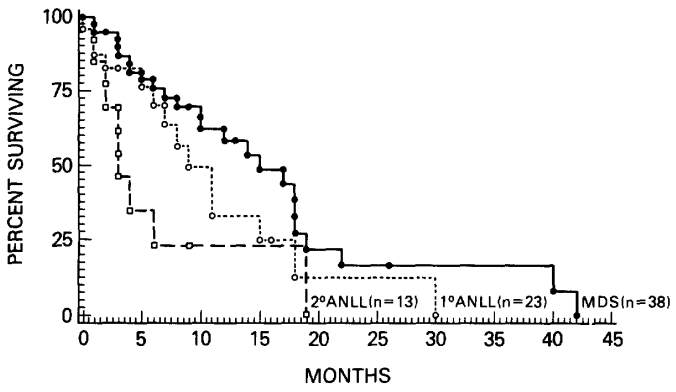

Fig 2. Kaplan-Meier estimates for the median duration of survival for 74 patients with 1°ANLL (open circles), 2°ANLL (open squares), and MDS (solid circles) treated with LoDAC.

That a differentiating agent such as ara-C could be considered for clinical trials was suggested by Lotem and Sachs in 1980.[7] While the concept of testing a putative differentiating agent in patients is provocative, correlative laboratory studies are crucial.

Even at low doses, ara-C is clearly cytotoxic; however, the data that suggest that differentiation may occur in vivo are sparse. In vitro assays for cellular differentiation were reported for only 76 patients (10%). Griffin et al,[40] using a colony-forming unit-granulocyte/macrophage (CFU-GM) agar assay reported that three patients with MDS who exhibited a "leukemic" growth pattern before LoDAC therapy demonstrated a "normal" growth pattern after therapy. Ishikura et al,[24] with a primary culture system, used the persistence of the pseudo–Pelger-Huet anomaly in the mature-appearing cells as evidence for differentiation. Apparent maturation of patient cells studied in vitro was also claimed by Michalewicz et al.[27] Using an implanted diffusion chamber assay system, both Hoelzer et al[41] and Moloney and Rosenthal[13] presented evidence for differentiation in selected patients, although the possibility of clonal selection was not ruled out. In contrast are the reports of Leyden et al,[26] Weisdorf et al,[33] and Weiss et al,[34] who interpreted their culture results as supporting a cytotoxic rather than a differentiating effect of LoDAC.

Similar controversy has been generated by the cytogenetic data, which were available to even a limited extent in 110 patients (15%). Hittleman et al[67] and Beran et al,[36] from the same institution, used the analysis of premature chromosome condensation to document that mature cells appearing posttherapy were derived from the malignant precursors. A few additional patients exhibited similar karyotypic abnormalities before therapy and after an apparent response to LoDAC.[40,42] Nevertheless, almost all of the other patients reported developed normal karyotypes with remission, and several reverted to the previous cytogenetic abnormality with relapse,[40,50,56,63,68] suggesting that clonal selection rather than differentiation had taken place.

In the majority of cases for which neither cytogenetic nor in vitro culture data are available to help distinguish cytotoxicity from differentiation, histopathologic observations have been used. Patients who achieved a remission in the absence of marrow hypoplasia are reported. However, this may simply reflect an inadequate frequency with which bone marrow samples are evaluated. Additional support for a maturational role for LoDAC is the slow, yet progressive rate with which mature cells begin to appear. Such subjective observations are not helpful in determining the potential differentiating activity of LoDAC.

Not only has there been inadequate testing of the differentiating activity of LoDAC in clinical trials, but there has been a failure systematically to evaluate the various routes of administration. In studies of the pharmacokinetics of LoDAC, Kufe et al[64] and Spriggs et al[65] recently demonstrated peak levels at 15 minutes after a bolus subcutaneous injection, with no detectable ara-C in the plasma at six hours. Additional data suggest similar pharmacokinetics for continuous infusions of the drug administered by either the intravenous or subcutaneous route.[55] Since the

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dose-time relationship (area under the curve) for the bolus and continuous infusion schedules may be similar, these investigators postulate that the high peak levels with the bolus may result in toxicity, whereas the continuous exposure is required for differentiation. To date, only 34 patients evaluable for response have been reported as being treated with a continuous infusion schedule, yet for patients with 1°ANLL, the response rates appear greater than with intermittent schedules. While the latter are obviously more convenient, it is possible that the therapy is inferior on a pharmacokinetic basis.

A number of clinical factors also add to the difficulty in interpreting the LoDAC data. Most investigators classify patients according to the FAB classification.[10,11] However, there is considerable variability in interpretation between investigators, and a revised scheme has recently been suggested to reduce the frequency of discrepancies.[69] Although we attempted to determine a correlation for MDS between FAB class and response to therapy, the number of patients in each group was too small and responses too infrequent for such an analysis. In addition, eligibility criteria often are not stated and response criteria are also not uniform among studies. Whenever necessary, patients were reclassified for the current analysis according to more widely accepted criteria. Since many publications provided neither response criteria nor objective laboratory data to substantiate a response, it is also possible that the response rates may be lower than presented. Finally, the clinical course of MDS is extremely variable, with median survival in some series in which patients were treated with supportive measures only, ranging from 1 year to more than 2 years.[12,70] While a response to therapy did not appear to prolong survival in the current analysis, only a randomized trial comparing LoDAC therapy to supportive care alone, such as the current study initiated by the Eastern Cooperative Oncology Group, can adequately address the clinical value of LoDAC.

The use of a differentiating agent such as LoDAC has generated considerable enthusiasm, as reflected by the large number of clinical studies reported using this treatment. Nevertheless, the data as presented do not identify the role for LoDAC in the treatment of MDS or ANLL. CR rates in MDS, secondary hematologic disorders, and miscellaneous hematologic malignancies of 16%, 16%, and 10%, respectively, do not support the use of LoDAC in those clinical situations. Although the response rate for patients with ANLL $\geq$ 50 years of age was 56%, this is based on only 61 cases. Fatal toxicity is lower than reported for elderly patients with conventional or even attenuated treatment programs for ANLL.[71] However, this must be viewed in light of the small sample sizes in the LoDAC trials and greater potential for selection bias. In a study of patients older than 60 years of age reported by Dutcher et al,[23] LoDAC had an inferior risk–benefit ratio when compared with a conventional regimen of ara-C and daunorubicin. Only studies with adequate numbers of patients that directly compare LoDAC with more conventional antileukemic therapy can resolve this question.

Unfortunately, the large body of available LoDAC data is difficult to interpret. Future clinical trials should be designed to determine the optimal dose and schedule of administration. Potentially less toxic regimens of ara-C using lower doses should be explored, and intermittent administration compared with a continuous infusion schedule. The mechanism of action of LoDAC could be evaluated with studies of cellular ara-CTP (ara-C triphosphate) levels, DNA synthesis, and inhibition by ara-C, comparing varying doses and schedules. Clinical trials should be carefully designed to correlate clinical response with in vitro measures of cellular differentiation. While there are few definitive markers of differentiation, current technologies include assays of premature chromosome condensation,[36,67] in vivo bromodeoxyuridine labeling,[72] and the sequential determination of differentiation antigens using recently developed monoclonal antibodies simultaneously with cytogenetic analysis.[73]

Once a regimen has been demonstrated to have clinical activity that correlates with in vitro differentiation, well-designed, multi-center randomized trials should be developed to test the efficacy of that regimen. Sample sizes should be adequate to identify patient populations that might benefit from LoDAC therapy. However, as currently used, LoDAC is associated with a low response rate, high incidence of severe toxicity, and lack of detectable effect on survival, and should therefore not be considered routine clinical practice.

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