Idarubicin and Standard-Dose Cytosine Arabinoside in Adults with Recurrent and Refractory Acute Lymphocytic Leukemia

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BACKGROUND. Drug resistance and early disease recurrence were major contributing factors in the limited survival of patients with acute lymphocytic leukemia (ALL). New chemotherapeutic agents and drug combinations were employed in refractory patients to overcome drug resistance.

METHODS. The current study evaluated the efficacy of a regimen comprising intravenous bolus injections of idarubicin, 12 mg/m^2 daily $\times$ 3, and a continuous 7-day infusion of cytosine arabinoside (ara-C), 100 mg/m^2 daily, in adults with refractory or recurrent ALL. Twenty patients aged 14–75 years were treated.

RESULTS. Six patients (30%) achieved complete remission (CR), 5 (25%) had a partial response (PR), and 9 (45%) did not respond. Recovery of blood counts occurred at a median of 20 days. One patient who achieved CR and one who achieved PR survived 1.5 and 2 years, respectively, after receiving this treatment. The median response and overall survival periods were 2.75 and 6.3 months, respectively. There was no relation between remission duration and previous chemotherapy. Neither leukocyte count at study entry nor patient karyotype was associated with attainment of CR. All patients experienced profound myelosuppression. Gastrointestinal toxicity was mild to moderate, with the exception of one case of World Health Organization Grade 3 mucositis.

CONCLUSIONS. The regimen of idarubicin and ara-C achieved a 55% overall response rate in patients with recurrent or refractory ALL. This response rate compared favorably with other regimens and was achieved with acceptable toxicity. Response duration was disappointing, however. ***Cancer* 2004;101:1414–9.**

KEYWORDS: idarubicin, cytosine arabinoside, acute lymphocytic leukemia, recurrent and refractory acute lymphocytic leukemia.

High doses of cytosine arabinoside (ara-C) in patients with refractory or recurrent acute lymphocytic leukemia (ALL) have achieved promising response rates of 40–60%, but difficulty remains in obtaining durable remissions in adult patients with recurrent ALL.[1–9]

Previous attempts to overcome the obstacle of resistance by increasing the doses of chemotherapeutic agents have often resulted in unacceptably severe side effects. Among these were studies involving various regimens of high-dose cytosine arabinoside (ara-C) and multiple doses and schedules of idarubicin, either as a standard daily dose of 12 mg/m^2 $\times$ 3 or as a single dose of 40 mg/m^2.[2,3,10–12]

The role of the standard 100 mg/m^2 per day $\times$ 7 dose and schedule of ara-C used in the treatment of acute myeloid leukemia (AML) has not been investigated in ALL. The current study describes

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TABLE 1
Patient Characteristics at the Time of Study Treatment

Characteristics	Current study	Giona et al.[2]	Testi et al.[3]
No. of patients (adults)	20	57	26
Gender			
Male	9	41	18
Female	11	16	8
Median age (range)	33 (14–75)	26.8 (15.6–48.2)	20 (15.5–44)
Diagnosis leukocyte count ($\times 10^6$/L) at the time of diagnosis			
Median (Range)	30,500 (2900–300,000)	N/A	N/A
Immunophenotype blasts (no. of patients)[32]	20	N/A	N/A
Pro B	2	N/A	(12[a])
Early pre-B	9	N/A	(12[a])
Pre-B	4	N/A	(12[a])
T-ALL	5	N/A	10
Cytogenetics (no. of patients)	17	N/A	N/A
t(9;22)(q34;q11)	3	N/A	3[b]
t(4;11)(q21;q23)	1	N/A	N/A
t(1;19)(q23;p13)	1	N/A	N/A
Hyperdiploid	1	N/A	N/A
Complex	3	N/A	N/A
Other abnormalities	2	N/A	N/A
Normal	6	N/A	N/A
Previous chemotherapy			
Anthracyclines	16	57	18
Others	4	0	8
Leukocyte count before study treatment ($\times 10^6$/L)			
Median (range)	14,000 (200–335,000)	6,400 (700–135,000)	N/A
Platelet count before study treatment ($\times 10^6$/L)			
Median (range)	103,350 (10,000–250,000)	N/A	N/A
Duration of first disease remission[c] (mos)			
Median (range)	7 (0–20)	13 (2–53)	11 (3–30)
BM recurrence upon entering study treatment			
First refractory	12	67	24
Second or more	8	21	2

T-ALL: T-lineage acute lymphoblastic leukemia; BM: bone marrow; N/A: not available.

[a] B-lineage.

[b] Philadelphia chromosome positive.

[c] Complete response is defined as no clinical or laboratory manifestation of leukemia.[15]

a pilot study of standard-dose idarubicin and ara-C for the treatment of recurrent and refractory ALL.

MATERIALS AND METHODS

Patient Selection

Our prospective study involved 20 consecutive, unselected patients with recurrent ALL (11 women and 9 men) with a median age of 33 years (range, 14–75 years). Twelve patients were in first recurrence of bone marrow disease and eight were in second (or subsequent) disease recurrence. Written, informed consent was obtained from all patients according to institutional regulations. All patients had a normal cardiac ejection fraction and normal liver function tests before study entry study.

Cytogenetic studies were successful in 17 patients. Six patients (30%) had a normal karyotype and 3 (15%) were Philadelphia chromosome positive. Other abnormalities included t(4;11)(q21;q23), t(1;19)(q23;p13), and hyperdiploidy, in one patient each. In three patients, more than three clonal abnormalities were observed (complex karyotype). By multiparameter flow cytometry, 15 patients were diagnosed with B-lineage ALL and 5 with T-lineage ALL. Biologic and clinical characteristics as well as the medical history of the patients (e.g., anthracycline exposure) are summarized in Table 1.

Treatment

Patients received an intravenous (i.v.) bolus dose of 12 mg/m^2 per day idarubicin on Days 1–3 and a 100 mg/m^2 per day continuous i.v. infusion of ara-C on Days 1–7. Bone marrow aspiration was performed before treatment and after peripheral blood count recov-

TABLE 2
Induction Treatment Results

Characteristics	Current study	Giona et al.[2]	Testi et al.[3]
Nadir leukocyte count after study treatment ($\times 10^6$/L)			
Median (range)	200 (100–800)	N/A	N/A
Nadir platelet count after study treatment ($\times 10^6$/L)			
Median (range)	20,000 (8000–46,000)	N/A	N/A
Nadir hematocrit after study treatment (%)			
Median (range)	22 (15–28)	N/A	N/A
Median time to granulocyte count $> 500 \times 10^6$	20	14	17
Median time to platelet count $> 50{,}000 \times 10^6$	10	13	22
Median time to hematocrit > 30%	13	N/A	N/A
Response to study treatment (no. of patients)			
Remission (CR + PR)	11	31[a]	18[a]
None	9	26	8
Response duration of all patients (mos)			
Median (range)	1.5 (0–18)	N/A	N/A
Response Duration of CR Patients (mos)			
Median (range)	3.5 (2–18)	N/A	N/A
Response Duration of PR patients (mos)			
Median (range)	3 (1–6)	N/A	N/A
Survival[b] of all patients (mos)			
Median (range)	4.5 (1–24+)	N/A	N/A
Survival[b] of CR patients (mos)			
Median (range)	7.5 (2–18)	N/A	N/A
Survival[b] of PR patients (mos)			
Median (range)	7 (6–24)	N/A	N/A

N/A: not available; CR: complete response; PR: partial response.

[a] CR: Complete response.

[b] Interval from start of study treatment to death.

ery. Standard G banding cytogenetic studies and immunophenotyping were performed on all bone marrow specimens. Peripheral leukocyte counts were obtained daily and leukocyte differential counts were manually performed at least twice weekly. Patients were treated in single standard hospital rooms with reverse isolation during periods of granulocytopenia. Sixteen patients (80%) received granulocyte-macrophage–colony-stimulating factor posttreatment as per physician choice. Platelet and red blood cell transfusions were given as necessary, and empiric broad-spectrum antibiotics were given for granulocytopenia and fever. The primary end point was response and the secondary end point was toxicity. All patients had peripheral blood recovery. Complete (CR) and partial responses (PR) were judged by previously published criteria.[13,14]

RESULTS

The overall response rate in the current study was 55% (Table 2). Six patients (30%) achieved a CR and 5 patients (25%) achieved a PR. Nine patients (45%) had progressive disease. Response duration, however, was short. The median duration of response for all patients was 1.5 months (range, 0–18 months). In comparison, response duration in responders (CR or PR) was 3 months (range, 1–18+ months). One patient with a CR was in continuous response for 18 months and one patient with a PR remained alive until 4 months after analysis of study results (Fig. 1).

Two of the four patients who had been treated with a non–anthracycline-containing regimen before participating in the study achieved a CR. In comparison, there were 4 CRs and 5 PRs in 16 patients who had previously been treated with anthracyclines. There was no meaningful association between response rate and age, cytogenetic data, duration of first CR, and the leukocyte count at the time of diagnosis. Four patients underwent allogenic bone marrow transplantation after achieving CR. Of these 4 patients, 1 died of transplant-related complications, 2 died of recurrent leukemia 3 and 6 months after the transplant, and 1 was alive when the study results were evaluated (September 2003), although she died 4 months later in January 2004. Three patients who achieved CR/ PR died because of early disease recurrence ($\leq$ 2 months). The other three responders underwent different consolidation/maintenance regi-

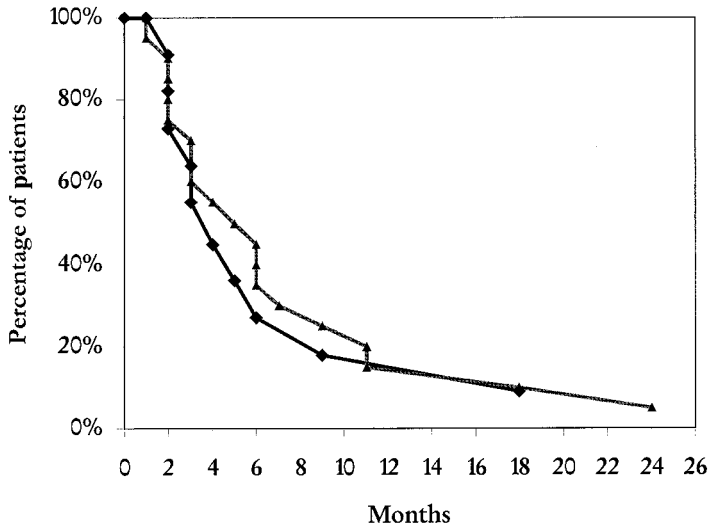

FIGURE 1. Life table comparative analysis plot of remission duration of responders and overall survival of all treated patients. Diamonds: duration of disease remission for responding patients; triangles: overall survival of all treated patients.

mens (one of them received idarubicin and ara-C for one extra cycle as a consolidation regimen). Patients were considered to be refractory after failing one or two cycles of therapy.

The median posttreatment nadir leukocyte count was 200 $\times$ 10^6/L (range, 100–800 $\times$ 10^6/L). The median time to a granulocyte count of $>$ 500 $\times$ 10^6/L was 21 days. The median nadir hematocrit was 22% (range, 15–28%). The median time to hematocrit $>$ 30% was 13 days. The median nadir platelet count was 20,000 $\times$ 10^6/L (range, 8000–46,000 $\times$ 10^6/L). The median time to a thrombocyte count $>$ 50,000 $\times$ 10^6 was 20 days.

Toxicity

All patients experienced bone marrow aplasia with severe granulocytopenia and thrombocytopenia during treatment with idarubicin and ara-C. Prolonged neutropenia resulted in 12 bacterial and 3 fungal infections. Nonhematologic toxicity was mild to moderate and included nausea and emesis, mucositis, diarrhea, and conjunctivitis. None of the patients had worse than World Health Organization (WHO) Grade 2 toxicites, except for one patient with Grade 3 mucositis, and all were relieved with supportive treatment. One patient developed elevated liver function test levels with hepatomegaly after treatment. Liver biopsy revealed chemical hepatitis secondary to ara-C and minimal leukemic infiltration. There were no cardiac events, despite previous treatment with anthracyclines in 16 patients. No renal toxicity was documented. Table 3 compares toxicities observed in our study with those published by others.[2,3]

DISCUSSION

The treatment of adult recurrent or refractory ALL remains a clinical challenge. Despite the use of new drugs and more aggressive treatment regimens, mortality for this category of patients remains high. With the exception of allogeneic stem cell transplantation, long-term leukemia-free survival is only $<$ 5 percent.[15] Anthracyclines (primarily daunorubicin) in combination with vinca alkaloids, steroids, and asparaginase are integral to most induction regimens for both adult and childhood ALL.[16] Wiernik et al. compared ara-C plus idarubicin with ara-C plus daunorubicin as induction and consolidation therapy for previously untreated adult patients with AML and concluded that ara-C plus idarubicin was superior.[17] In a separate randomized trial, Berman et al.[18] similarly showed that patients with de novo AML who had received idarubicin and ara-C had a superior response compared with those who had received standard treatment with daunorubicin and ara-C. Although the role of idarubicin in the treatment of patients with newly diagnosed[19–24] and refractory AML[1,25–28] is well established, it has been less well studied for the treatment of ALL. Studies by Weiss[10] and Giona et al.[2] showed that a combination of high-dose ara-C and an anthracycline had a greater likelihood of achieving a first CR in patients with refractory ALL or a second CR in patients with recurrent disease than reinduction with standard vincristine, prednisone, and anthracycline-based regimens. Weiss et al.[29] studied a regimen that contained high-dose ara-C and a single high dose of idarubicin as salvage induction therapy for patients with recurrent or refractory ALL. The CR rate was 38%, with moderate but acceptable toxicity. Drug resistance proteins, such as P-glycoprotein and *bcl*-2, may con-

TABLE 3
Nonhematologic Toxicity

Side effects	WHO 3	WHO 4	Grade 3 or 4 cases (%)
Nausea and emesis			
Current Study	0	0	0.0
Giona et al.[2] (idarubicin × 3 doses and high-dose cytosine arabinoside of 3 g/m^2 × 6 doses)	2	0	2.3
Testi et al.[3] (idarubicin × 1 dose and high-dose cytosine arabinoside of 3 g/m^2 × 5 doses)	N/A	N/A	N/A
Mucositis			
Current study	1	0	5.0
Giona et al.	14	1	17.1
Testi et al.	5	2	10.0
Diarrhea			
Current study	0	0	0.0
Giona et al.	2	0	2.3
Testi et al.	6	3	12.9
Hepatic toxicity			
Current study	1	0	5.0
Giona et al.	4	1	5.7
Testi et al.	3	2	7.1
Renal toxicity			
Current study	0	0	0.0
Giona et al.	0	1	1.1
Testi et al.	3	0	4.3
Cardiac toxicity			
Current study	0	0	0.0
Giona et al.	1	1	2.3
Testi et al.	1	0	1.4
Neurologic toxicity			
Current study	0	0	0.0
Giona et al.	1	1	2.3
Testi et al.	1	0	1.4
Hyperglycemia			
Current study	0	0	0.0
Giona et al.	2	0	2.3
Testi et al.	N/A	N/A	N/A

WHO: World Health Organization.

tribute to a worse outcome. Del Principe et al.[30] reported that P-glycoprotein and *bcl*-2 levels predict outcome in adult ALL. In vitro and in vivo data suggest that idarubicin is less susceptible to P-glycoprotein–mediated drug efflux than daunorubicin, suggesting that idarubicin could be used to overcome drug resistance in leukemic cells.[31,32] In fact, Nuessler et al.[32] showed the efficacy of idarubicin monotherapy in multiply pretreated patients with leukemia.

Idarubicin and ara-C in various combinations have been used in the treatment of refractory or recurrent ALL for more than a decade.[3,11,12] Giona et al.[2] emphasized the importance of leukocyte counts at the time of diagnosis and the association of the duration of first CR of patients treated at first recurrence with final outcomes. Other studies stressed the relation between patient cytogenetics and immunophenotyping and disease outcome, especially the significance of CD10 positivity and the presence of t(9;22).[10,31,33–34] Although in our study of 20 patients, there was no meaningful association between response rate and any of the above mentioned criteria.

Contrary to previously published studies, we treated patients with refractory and recurrent ALL with an i.v. bolus injection of idarubicin 12 mg/m^2 daily × 3 and a continuous 7-day infusion of ara-C 100 mg/m^2 daily. Our study's response rate of 55% (CR 30% and PR 25%) was similar to that of the high-dose studies, but our patients may have tolerated the standard dose treatment better and with fewer side effects. Except for moderate elevations of liver functions in one patient and WHO Grade 3 mucositis in another patient, extrahematologic toxicity was acceptably mild. Profound myelosuppression occurred in 18 patients and was one of the major causes of death. Fatal infection, early disease recurrence, and short disease remission duration eliminated the possibility of further treatments such as stem cell transplant.

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