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Idarubicin in Sequential Combination with Cytosine Arabinoside in the Treatment of Relapsed and Refractory Patients with Acute Non-lymphoblastic Leukemia

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Abstract—*Sixteen adult patients with refractory acute non-lymphoblastic leukemia (ANLL) underwent reinduction therapy with idarubicin (12 mg/m^2) i.v. on days 1–3) followed by cytosine arabinoside (120 mg/m^2 every 12 h on days 4–10). Patients achieving complete remission (CR) received consolidation and early intensification courses which included idarubicin at lower dosage. CR was reached after a single course in 70% of the patients treated at first relapse, and two of the five subjects previously resistant to daunorubicin-containing regimens responded to the idarubicin protocol. The median duration of CR was 11 months. Gastrointestinal side-effects were not important; mild and reversible ECG changes were noted whereas delayed cardiac toxicity was not observed despite previous treatment with daunorubicin. These encouraging results confirm the efficacy of idarubicin in treating acute leukemia and suggest it may have a major role in the treatment of relapsed and refractory patients with ANLL.*

INTRODUCTION

FOR MANY years the main drugs in the treatment of acute non-lymphoblastic leukemia (ANLL) have been the anthracycline antibiotics doxorubicin (DX) and daunorubicin (DNR). In combination with cytosine arabinoside (ARA-C) they induce complete remission (CR) in 60–85% of previously untreated patients [1]. Many efforts are now being made to find a more adequate treatment both for the patients still resistant to conventional induction therapy and for the subjects who relapse within 1–2 years. In fact in the latter group, second CR are rarely achieved with the drugs used at first diagnosis and, when second CR is obtained, disease-free survival is generally brief. During recent years new treatments for relapsed and resistant ANLL have included intensive reinduction chemotherapy and the use of new antileukemic agents. One of the latter, idarubicin (4-demethoxy-daunorubicin, 4-DMDR, IMI-30, NSC 256439), a new derivative of DNR, was introduced because of its higher anti-tumor activity in experimental leukemias and lower cardiac toxicity compared with DNR and DX [2, 3]. In human beings, phase I and II clinical studies [4] have already shown that idarubicin as a single agent or in combination with other drugs has a significant antileukemic effect with minor toxicity. These initial clinical findings are confirmed by the results of the study reported here of a group of adult patients with relapsed or primarily resistant ANLL treated with idarubicin in sequential combination with ARA-C.

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MATERIALS AND METHODS

From March 1984 to December 1985, 16 hospitalized adults with previously treated ANLL classified according to the FAB criteria participated in this study. Clinical follow-up for the present evaluation was continued until May 1986. Patient characteristics and pathological data are shown in Table 1: the 11 patients in first relapse included a subject who had a relapse 3 months after an allogeneic bone marrow transplant performed during CR. A second group of five patients was considered to be treatment-resistant since they did not respond to conventional chemotherapy administered at the onset of their disease. The drugs received previously

Table 1. Characteristics of 16 patients with relapsed and refractory ANLL

Sex	
Female	9
Male	7
Age (years)	
Range	15–64
Median	44
Morphology (FAB)	
M_1–M_2	9
M_3	3
M_4–M_5	4
Phase of the disease	
First relapse after chemotherapy (median duration of first CR = 18 months)	10
Relapse 3 months after allogeneic BMT	1
Primarily chemotherapy-resistant	5

Treatment protocol

All patients received a cycle of idarubicin 12 mg/m^2 daily in i.v. bolus for 3 consecutive days (days 1–3), followed by ARA-C at a dosage of 120 mg/m^2 given by 1-h i.v. infusion every 12 h for 14 doses (days 4–10). If a partial remission (PR) was obtained a second course of treatment was prescribed.

On attaining CR patients started consolidation treatment consisting of two courses of idarubicin 10 mg/m^2 daily i.v. for 2 consecutive days followed by ARA-C 100 mg/m^2 every 12 h from days 3–7. Early intensification treatment was then given each month for 6 months consisting of alternate courses of vincristine plus intermediate-dose ARA-C and idarubicin plus VP-16. Support therapy consisting of antibiotics and blood products was administered when required.

Performance status was considered sufficient for a new therapeutic attempt in all patients. Pretreatment evaluation included a hemogram, bone marrow aspirate, biochemical and enzymatic profile, ECG and chest X-ray. During and after therapy

Table 2. Previous chemotherapy administered in 11 ANLL patients in first relapse and in five resistant to DNR-containing regimens

Case No.	FAB	Previous chemotherapy: Induction	Consolidation	Maintenance	Cumulative DNR dosage > 600 mg/m^2	Duration of CR	Outcome to reinduction with IDA + ARA-C
Patients in first relapse							
1	M2	DNR,ARA-C,TG	ADM,VCR,ARA-C	DNR,ARA-C,TG,VCR,DMZ	Yes	4 years	CR
2	M2	DNR,ARA-C,TG	ADM,VCR,ARA-C	DNR,ARA-C,TG,VCR,DMZ	Yes	3 years	CR
3	M4	DNR,ARC-C,TG	ADM,VCR,ARA-C	DNR,ARA-C,TG,VCR,DMZ	Yes	3 years	CR
4	M4	DNR,ARA-C,TG	ADM,VCR,ARA-C	DNR,ARA-C,TG,VCR,DMZ	Yes	4 years	Aplastic death
5	M3	DNR	DNR	DNR,ARA-C	Yes	2 years	CR
6	M3	DNR	DNR	DNR,ARA-C	—	10 months	Resistance
7	M3	DNR	DNR	—	—	3 months	Resistance
8	M1	IDA,ARA-C	IDA,ARA-C	DNR,ARA-C,VCR	—	1 year	CR
9	M5	IDA,ARA-C	IDA,ARA-C	DNR,ARA-C,VCR	—	1 year	CR
10	M2	IDA,ARA-C	IDA,ARA-C	—	—	6 months	CR
11	M4	DNR,ARA-C,TG	DNR	DNR,ARA-C,BMT	Yes	3 years	Aplastic death
Resistant patients							
12	M2	DNR,ARA-C	—	—	—	—	CR
13	M2	DNR,ARA-C	—	—	—	—	Resistance
14	M2	DNR,ARA-C	—	—	—	—	Aplastic death
15	M1	DNR,ARA-C	—	—	—	—	CR
16	M4	IDA,ARA-C	—	—	—	—	Resistance

DNR: daunorubicin; ADM: adriamycin; ARA-C: cytosine arabinoside, IDA: idarubicin; TG: thioguanine; VCR: vincristine; PDR: prednisone; DMZ: dexamethasone; BMT: allogeneic bone marrow transplantation.

by the patients are summarized in Table 2: four patients had already been treated with idarubicin (10 mg/m^2 daily × 3 days) which, however, had been administered simultaneously with ARA-C (200 mg/m^2 daily infusion × 5 days) according to a protocol originally proposed by Memorial Sloan Kettering Cancer Center [5]. The median duration of the first CR in relapsing patients was 18 months; in six subjects of this group the total previous DNR dosage was over 600 mg/m^2.

patients were monitored with a daily peripheral blood count, and weekly ECG and renal and hepatic function tests; bone marrow aspirates were obtained every 3 weeks to assess response to chemotherapy.

Evaluation criteria

A patient was considered to be in CR when bone marrow examination showed a complete recovery of hemopoiesis with less than 5% blast forms and

Table 3. Therapeutic efficacy of reinduction treatment with idarubicin and ARA-C in 16 patients with relapsed and refractory ANLL

	No. of patients	CR No.(%)	Aplastic death No.(%)	Resistance No.(%)
First relapse after chemotherapy	10	7 (70)	1 (10)	2 (20)
Relapse after allogeneic BMT	1	—	1	—
Primarily chemotherapy-resistant	5	2 (40)	1 (20)	2 (40)
Totals	16	9 (56.25)	3 (18.75)	4 (25.00)

Median time for achievement of CR = 33 days (range 27–37).
Peripheral leukocytes nadir = 10th day (range 7–20).

normal peripheral blood count (PMN>1500/mm^3 and platelets >100,000/mm^3), and in PR when there were 5–15% blasts in the bone marrow with normal peripheral blood.

Patients were defined as resistant if they showed an inadequate clearing of bone marrow leukemic cells or regrowth of marrow blasts after recovery from aplasia or if CR lasted less than 1 month. Patients who died before the end of the induction course or during the aplastic post-treatment phase without evidence of residual leukemia were considered treatment failures as regards the CR rate.

The duration of response was measured from the day CR was documented to the day when a relapsing marrow was observed.

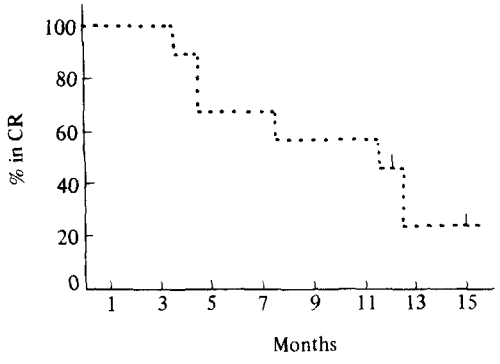

Fig. 1. Duration of CR in nine relapsed and refractory ANLL patients submitted to consolidation and intensification courses. The vertical lines on the curve indicate subjects still in CR.

RESULTS

Bone marrow aplasia and profound peripheral pancytopenia were documented in all the patients; the lowest peripheral leukocyte count (range 10–700 cells/mm^3) was reached 7–20 days after starting therapy.

As reported in Table 3, nine patients (56%) reached CR after a single reinduction course; most of them (70%) were in the relapsing group although two (40%) were subjects previously resistant to a classical DNR and ARA-C protocol. Three patients in relapse after treatment with idarubicin administered simultaneously with ARA-C (Table 2) had a new CR with the sequential combination of the two drugs. No PR was observed; three patients died within 3 weeks while still aplastic, and four were classified as resistant.

Figure 1 shows the remission duration data for the nine patients who were placed on consolidation and intensification therapy. The median duration of CR was 11 months. Fatal infections occurred in two patients at 3 and 7 months during the aplastic phase induced respectively by consolidation and early intensification treatment; five patients had a bone marrow relapse; two patients are still alive and disease-free at 11 and 14 months from the time of achieving CR.

Concerning the side-effects observed during induction and consolidation treatment, alopecia could not be evaluated because of previous chemotherapy; there was a low incidence of gastrointestinal discomfort and in particular stomatitis was rarely observed. In spite of previous treatment, none of the patients presented clinical symptoms of liver failure; however SGOT of over 100 U/l and total bilirubin of over 3 mg% were noted in seven cases. These abnormal liver function tests were usually observed within 7–10 days after the end of induction or consolidation courses; the values returned to normal in 1 month without serological evidence of viral infections. T-Wave changes at ECG were present in about 30% of the cases but were all rapidly reversible; no clinical symptoms of delayed cardiotoxicity were observed even in the group of patients who had previously received over 600 mg/m^2 DNR.

DISCUSSION

One object of modern pharmacological research is to discover antileukemic agents that are more

effective both with respect to disease cure and in the treatment of relapses. The use of idarubicin, one of the anthracycline compounds developed during recent years, has been proposed to clinicians who are finding that this new DNR derivative is an effective agent for the treatment of ANLL. As a single agent the effective dose was established at between 30 and 45 mg/m^2 per course, which at Memorial Sloan Kettering Cancer Center [5] produced five CR in 28 patients with pretreated ANLL. The dose was cut to 8 mg/m^2 daily for 5 consecutive days by Harousseau *et al.* [6] who obtained 50% CR in 12 ANLL patients in first relapse.

Subsequently idarubicin has been used in combination with other antileukemic agents, in particular ARA-C [4, 5, 7]. In the present study 70% CR in a group of adult patients with ANLL in first relapse was obtained after a single course of idarubicin in sequential combination with ARA-C; the CR rate was 56% if we include five subjects who were primarily chemotherapy-resistant. In the trial conducted at Memorial Sloan Kettering Cancer Center [5] a CR rate of 23% was observed in pretreated ANLL subjects who received idarubicin 10 mg/m^2 for 3–4 days administered simultaneously with ARA-C 25 mg/m^2 i.v. bolus followed by 200 mg/m^2 continuous infusion daily for 5 days.

The above findings suggest that idarubicin, at the optimal dose of 36–40 mg/m^2 per course subdivided in 3 consecutive days, combined with ARA-C, is effective in ANLL relapsing patients who previously received traditional anthracyclines. Furthermore, in our opinion, the administration of the two drugs according to a sequential schedule might increase the effectiveness of idarubicinol, an idarubicin metabolite characterized by longer plasma half-life and by antileukemic activity similar to the parent compound [8]. However, only pharmacokinetics and randomized clinical studies will show if the efficacy of sequential administration is really greater than that of daily simultaneous infusion of idarubicin and ARA-C.

Although the treatment of ANLL in relapse is still difficult, the recent introduction of new drugs and the use of intensive combination therapies produce second remissions in almost half the cases [1, 9]. Using massive doses of ARA-C with and without anthracycline antibiotics CR rates of 63% and 66%, respectively, were reached in relapsing ANLL patients who were also resistant to conventional ARA-C doses [10]. However, in all these studies the median duration of CR after the reinduction phase, whether followed by conventional maintenance therapy or not, was generally brief, varying between 4 and 6 months, with only 10% of the patients surviving for 1 year. The longer duration of 11 months obtained in our study underlines that the inclusion of new antileukemic agents like idarubicin, in either the reinduction or consolidation phases, could be helpful in prolonging CR duration in refratory ANLL. Moreover, the fact that CR was also obtained in two patients who had failed to respond to previous induction attempts with regimens containing DNR further confirms the antileukemic potency of idarubicin. Although it is difficult to define resistance to traditional anthracyclines, our findings indicate that idarubicin is probably not cross-resistant with DNR or DX, thus supporting the experimental data [11] and previous clinical observations [12].

Idarubicin was proposed for clinical trials not only because of its greater antitumor activity but also because of its low cumulative cardiotoxicity [2]. The latter should be confirmed in the near future by randomized clinical trials still in progress on previously untreated patients [5, 13], some over 55 years of age [14]. In our present study only mild and reversible ECG changes were observed which did not correlate with the previous administration of DNR which in six patients exceeded a total dosage of 600 mg/m^2. However, a more accurate cardiologic evaluation is desirable in these patients to better investigate anthracycline cumulative cardiotoxicity. As regards other extrahematological toxicities, idarubicin appeared to be similar to DNR and DX although gastrointestinal side-effects were less important.

In conclusion, our study demonstrates the role of idarubicin in the treatment of refractory ANLL. Moreover, since this new DNR derivative seems also to prolong CR duration, it could be proposed as an alternative to more intensive chemotherapy such as regimens including high-dose ARA-C that might represent a risk due to their serious extrahemopoietic toxicity [15].

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