4-Demethoxydaunorubicin (Idarubicin) in Refractory or Relapsed Acute Leukemias

A Pilot Study

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Twenty-five adults with previously treated acute leukemia were treated with 4-demethoxydaunorubicin (Idarubicin) with a daily dose of 8 mg/m^2 for 3 days intravenously. Complete remission was achieved in 3 of 18 patients with acute nonlymphoblastic leukemia (ANLL) and 2 of 6 with lymphoblastic leukemia. Complete remissions were observed in two of eight ANLL patients refractory to cytarabine, anthracycline, and m-Amsa (amsacrine), indicating a lack of cross-resistance between these drugs and Idarubicin. The median duration of remission was 8 weeks. The main major toxicity of Idarubicin therapy, severe myelosuppression, cannot be considered a toxic effect because it was desired in this case list. Our preliminary results indicate that Idarubicin has significant activity against refractory adult acute leukemia.

Cancer 55:1452–1454, 1985.

DESPITE encouraging results in the treatment of newly diagnosed patients with acute leukemia,[1,2] the outlook for refractory or relapsed patients is still poor. Thus, the development of effective therapy for refractory and relapsed patients presents a major problem. Among the new anti-leukemic agents studied over the last few years is 4-demethoxydaunorubicin (Idarubicin). Thus drug, synthesized in the Farmitalia Carlo Erba Research Laboratories, Milan, Italy, is a new anthracycline analog that lacks the methoxyl group in position 4 of the daunorubicin (DNR) aglycone.[3] In experimental leukemias this drug was eight times more potent than DNR and five times more potent than doxorubicin.[4,5] Idarubicin can be given orally with proven anti-leukemic activity.[6] DNR and Idarubicin have a similar mechanism of action,[7] although Idarubicin is less cardiotoxic.[4,8] The compound is now in Phase II clinical investigation and evidence of therapeutic efficacy has been obtained in leukemia, with the major indication from studies in animals.[9,10]

Reported here are 25 patients with refractory or relapsed acute leukemia, treated with Idarubicin.

Materials and Methods

Between January 1983 and January 1984 a total of 25 previously treated adult patients with acute leukemia entered the study. 16 were men and 9 were women, with a median age of 34 years (range, 18 to 62). Six patients had acute lymphoblastic leukemia (ALL), 18 had acute nonlymphoblastic leukemia (ANLL), and 1 had chronic myelogenous leukemia in blast crisis (BC-CML).

All cases had previously received conventional chemotherapy. Our induction therapy for ALL included a combination of vincristine, doxorubicin, prednisolone, and L-asparaginase,[11] and a regular "7 + 3 protocol" for ANLL.[12] Refractory ANLL patients were given second-line chemotherapy with the combination amsacrine + 5-azacytidine ± etoposide.[13] Ten ANLL patients who had relapsed on conventional chemotherapy received Idarubicin as second-line chemotherapy and eight as third-line therapy after failure of reinduction therapy with amsacrine alone or combined with 5-azacytidine ± etoposide.

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Accepted for publication April 30, 1984.

Dosage Schedules

Idarubicin was supplied by Farmitalia Carlo Erba, Milan, Italy. In all cases the drug was employed at the dose of 8 mg/m^2/day for 3 days intravenously. Bone marrow examinations were made on day 10 or 11 and once weekly. If there was no reduction of the leukemic infiltrate 2 to 3 weeks after the first course, a second course of treatment was given with no escalation of the dosage. A minimum of two courses of treatment was needed for a patient to be evaluable for response. Before and after Idarubicin, all patients were evaluated by electrocardiogram (ECG) and echocardiography. Complete blood counts were obtained daily; liver and renal functions, including serum electrolytes, were checked weekly. Supportive care with erythrocyte and platelet transfusions and antibiotics was provided when indicated.

Criteria of Response

Complete remission (CR): recovery of normal hematopoiesis with less than 5% blasts accompanied by recovery of peripheral blood counts to at least 2000 leukocyte count/mm^3 and 100,000/mm^3 platelets.

Partial remission (PR): similar recovery of peripheral blood counts accompanied by significant reduction in the bone marrow blast infiltrate, but still showing more than 5% and less than 50%.

After remission, patients received maintenance chemotherapy with 2 to 3 courses of Idarubicin at the same dosages as in induction. The duration of remission was measured from the time the remission was documented to the time of first evidence of relapse.

Results

Table 1 summarizes the results with Idarubicin and shows patients' clinical data and responses to Idarubicin. Four ALL patients achieved a response and two obtained a CR. No response was obtained in the CML-BC patient, and 50% response (CR + PR) was achieved in ANLL patients. Two responders (one ALL and one ANLL) who had an histocompatibility antigen (HLA) compatible donor were given a bone marrow transplant and are alive in CR 4$^+$ to 10$^+$ months from therapy with Idarubicin. The peripheral blasts generally disappeared by 7 days and bone marrow aplasia occurred within 2 weeks. Two of five CR were achieved after a single course of Idarubicin therapy, the other after the second course. The median duration of CR was 8 weeks (range, 4 to 36 weeks) with two patients remaining in remission at the last follow-up (both had received bone marrow transplant). The median duration of PR was 2 weeks, with a range of 1 to 4 weeks.

TABLE 1. Results Obtained with Idarubucin in Acute Leukemia

Diagnosis	No. of patients	CR	PR	NR
ALL	6	2	2	2
ANLL	8*	2	2	4
	10†	1	4	5
BC-CML	1			1
Total	25	5 (20%)	8	12
CR + PR		13/25 (52%)		

* Refractory cytarabine + anthracyclines and amsacrine + etoposide.
† Relapsed to cytarabine + anthracyclines.
CR: complete remission; PR: partial remission; NR: no response; AL: acute lymphoblastic leukemia; ANLL: acute nonlymphoblastic leukemia; BC-CML: chronic myelogenous leukemia in blast crisis.

Toxicity

All responsive patients experienced intense myelosuppression. One patient died during this period and five experienced serious systemic infections within 4 weeks of starting Idarubicin therapy. Table 2 summarizes other toxic effects, which were rare and generally transient. In no case were cardiac rhythm disturbances observed.

Discussion

The introduction of cytarabine and anthracyclines represented the first major advance in the therapy of acute nonlymphoblastic leukemia. When these drugs are used as single agents in untreated patients, a remission rate of 30% to 40% has been observed.[14,15] The combination has resulted in doubling of the CR rates and it is now possible to obtain 70% to 80% responsive patients.

Despite this progress, the median duration of CR is generally about 12 months. Because approximately 80% to 90% of patients relapse within 2 years, the development of new anti-leukemic drugs is urgent.

TABLE 2. Toxicity in 25 Patients Treated with Idarubicin (NCOG Criteria)*

	Grade				
	0	1	2	3	4
Nausea and vomiting	23	1	1		
Hepatic					
Bilirubin, alkaline phosphatase	22	1	2		
SGOT, SGPT	22	3			
Infection	19			5	1
Cardiac	25				
Mucositis	25				

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SGOT: serum glutamic oxalocetic transaminase; SGPT: serum glutamic pyruvic transaminase.

A response rate of 52% (CR + PR) in a group of patients, most of whom had already failed to respond to two to three treatment regimens, suggests that Idarubicin has potent anti-leukemic activity. The response rate with Idarubicin is identical to that with m-Amsa (amsacrine)[16,17] and is clearly superior to the response rate (11%) observed with doxorubicin in a group of similar patients.[18] Moreover, our results in terms of CR ($^2/_6$ for ALL and $^3/_{18}$ for ANLL) are in good agreement with the data of Young *et al.*[10] who reported about 30% CR for ALL and about 16% for ANLL.

The most significant aspect of the anti-leukemic activity of Idarubicin is that CR can be induced in patients who have already received extensive treatment, many of whom have become refractory to all available agents. Furthermore, 4 of 8 patients who were resistant to primary- and second-line chemotherapy achieved remission with Idarubicin, suggesting an apparent lack of cross-resistance with drugs known to be active in acute leukemia. Although most responses in this study were in ANLL patients, there was certainly sufficient activity in the limited number of patients with ALL to warrant further investigation of the activity of Idarubicin in this disease. In addition, two responsive patients with an HLA compatible donor were given a bone marrow transplant and are now living in CR.

In spite of the large doses used, Idarubicin was tolerated very well. In no case was acute toxicity observed compared to the other anthracyclines, which have a significant incidence of acute gastrointestinal toxicity. Cardiac toxicity was not observed in spite of the fact that all patients had also received other drugs such as anthracyclines and m-Amsa. The main effect of Idarubicin was on bone marrow, which is the most desirable effect for an anti-leukemic agent. The lack of toxicity on other organs and the optimal effect on bone marrow makes Idarubicin a unique drug for the treatment of acute leukemia.

In conclusion, the discovery of Idarubicin appears to contribute a significant advance, promising improved prognosis in leukemic patients refractory or relapsed to first- or second-line chemotherapy.

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