[CANCER RESEARCH 50, 6833-6835, November 1, 1990]

Phase II Study of Oral Idarubicin in Favorable Histology Non-Hodgkin's Lymphoma[1]

Delvyn C. Case, Jr.,[2] Daniel M. Hayes, Marjam Gerber, Richard Gams, Thomas J. Ervin, and Brian M. Dorsk

Divisions of Hematology and Oncology, Department of Medicine, Maine Medical Center, Portland, Maine 04102 [D. C. C., D. M. H., T. J. E., B. M. D.], and Adria Laboratories, Columbus, Ohio 43216 [M. G., R. G.]

ABSTRACT

Idarubicin, a new analogue of daunorubicin, was administered p.o. for 3 consecutive days every 3 weeks at a dose of 45 mg/m² in 46 patients (45 eligible and evaluable) with previously treated, favorable histology, non-Hodgkin's lymphoma. Median clinical characteristics included an age of 66 years, a performance status of 1, and one prior chemotherapeutic regimen. Forty-one patients were relapsing from prior therapy, and 37 had stage IV disease. Patients with prior anthracycline therapy were excluded.

Responses were observed in 58% of patients (10 complete and 16 partial), with a median duration of 6+ months (2–41+ months). Idarubicin was well tolerated. Nonhematological toxicities (nausea/vomiting, mucositis/diarrhea, alopecia, and anorexia) were observed in ≤50% of patients. Median hematological values during the first cycle include a WBC of 4100/mm³ and a platelet count of 147,000/mm³. With dose escalation, hematological toxicity was the dose-limiting toxicity. Symptomatic cardiac toxicity was not observed. Median values for the resting left ventricular ejection fraction during the course of therapy were 0.65 (initial) and 0.63 (final). Idarubicin in oral form is an active drug in previously treated patients with favorable histology non-Hodgkin's lymphoma.

INTRODUCTION

Anthracyclines are important drugs for the treatment of lymphoma. Idarubicin (4-demethoxydaunorubicin) is a new anthracycline that is active by both p.o. and parenteral routes of administration (1). Idarubicin is more active than daunorubicin and doxorubicin in L1210 and Gross leukemia, T-lymphoma EL4, and J744 lymphoma (2). Preclinical toxicological studies have suggested an increased therapeutic index of idarubicin compared to daunorubicin and doxorubicin, particularly as regards cariotoxicity (2). In phase I trials, gastrointestinal side effects and alopecia were seen less often than with daunorubicin and doxorubicin; tumor responses were observed in patients with non-Hodgkin's lymphoma (3, 4).

Idarubicin has been the subject of two studies in lymphoma and Hodgkin's disease (5, 6). Based upon the results of these studies, a phase II study of p.o. in previously treated patients with favorable histology lymphoma was developed.

MATERIALS AND METHODS

Requirements for entry into this study included histological confirmation of stage II B, III, or IV low-grade (favorable history) non-Hodgkin's lymphoma (working formulation) (7) or one of the following types of lymphoma by the Rappaport classification (8): nodular, poorly differentiated lymphocytic lymphoma; diffuse, well-differentiated lymphoma; or nodular, mixed, histiocytic-lymphocytic lymphoma. Patients had previously been treated with chemotherapy (one or two prior programs), had not received prior anthracycline or anthracenedione, had a performance status of 0–2 (Eastern Cooperative Oncology Group), were ≥18 years old, had bidimensionally measurable disease, had a WBC of ≥4,000/mm³, and had a platelet count of ≥100,000/mm³ (unless there was bone marrow involvement). The bilirubin was <2.0 mg/100 ml, the creatinine was <2.5 mg/100 ml, and the resting radionuclide ejection fraction was ≥0.50. Written informed consent was obtained.

Pretreatment evaluation included history, physical examination, performance status, weight, height, and tumor measurements. Laboratory procedures performed were complete blood count with platelet count, urinalysis, and sequential multianalyzer survey (blood urea nitrogen, creatinine, uric acid, bilirubin, serum glutamic oxaloacetic transaminase, and alkaline phosphatase). An electrocardiogram, chest X-ray, and chest and abdominal computerized axial tomogram were obtained. Bone marrow biopsies were done in two patients, and the radionuclide ejection fraction was determined.

Clinical findings were evaluated at each patient visit. Radiographic studies were repeated after each two cycles to define response and duration. Complete blood counts with platelet counts were performed weekly during the first two cycles and thereafter on the day of therapy. Chemistries were repeated every 6 weeks. Cardiac function was assessed by determination of the resting radionuclide ejection fraction prior to the first dose of therapy, and this measurement was repeated when the cumulative dose of idarubicin reached 200–250 mg/m² and 400–450 mg/ms2 and at the end of therapy or when the study was terminated because of relapsing/progressive disease. Significant changes in ejection fraction were defined according to the method of Alexander *et al.* (9).

A CR[3] was defined as the clinical and X-ray disappearance of all detectable disease for a minimum of 4 weeks without the appearance of any new lesions. A PR was defined as a 50% or greater reduction in the sum of the products of the maximal perpendicular diameters of all measurable lesions for at least 4 weeks without the appearance of any new lesions.

No change was defined as decrease in tumor masses of less than 50% or increase of less than 25% lasting for at least 4 weeks. Progressive disease was defined as increase in the size of a measured lesion by at least 25% or the appearance of any new lesion.

Idarubicin was supplied by Adria Laboratories (Division of Erbamont, Inc., Columbus, OH) in 5- and 10-mg capsules. The initial dose of idarubicin in this study was 45 mg/m² p.o. divided into three single daily doses (15 mg/m²/day p.o.) on an empty stomach on three sequential days. All patients received metoclopramide (10 mg) 1.5 h before each dose of idarubicin and 10 mg 6 hours after each dose of idarubicin).

Therapy was repeated every 3 weeks if there was adequate bone marrow recovery (WBC ≥ 3500/mm³ and/or granulocyte count ≥ 1500/mm³ and platelet count of 775,000/mm³). Dose adjustments were made as shown in Table 1. Chemotherapy was reduced or discontinued because of the development of unacceptable/uncontrollable gastrointestinal side effects, prolonged hematological suppression, or unexpected other-organ toxicity. Therapy was discontinued if the ejection fraction fell to <0.50.

A minimum of two courses was required to be considered an adequate trial for evaluation of efficacy unless there was rapid progression (>50% increase in tumor size). Responding patients (CR and PR) received therapy for 1 year or until progression. Patients showing no change

Received 4/9/90; accepted 7/31/90.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] Presented in part at the 81st Annual Meeting of the American Association for Cancer Research, Inc., Washington, DC, May 23–26, 1990.

[2] To whom requests for reprints should be addressed.

[3] The abbreviations used are: CR, complete remission; PR, partial remission; EF, ejection fraction.

Table 1 *Dose adjustments for idarubicin based upon hematological toxicity*

WBC nadir (cells/mm³)		Granulocyte nadir (cells/mm³)		Platelet nadir (×10³/mm³)	Next dose
>2,000	and/or	>1,000	and	>75	Increase total dose by 5 mg/m²
1,000–2,000	and/or	500–10,000	and	50–75	Same dose
<1,000	and/or	<500	and/or	<50	If no fever or infection and if counts recovered by day 21, decrease total dose by 5 mg/m²
<1,000	and/or	<500	and/or	<50	If fever or infection or no recovery by day 21, decrease total dose by 10 mg/m²
<500	and/or	<250	and/or	<25	Decrease total dose by 10 mg/m²

were treated for six cycles. Patients progressing were taken off study after two courses of therapy.

Characteristics of patients participating in this study are summarized in Table 2. Prior treatment included cyclophosphamide or chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; and 1,3-bis(2-chloroethyl)-1-nitrosourea, cyclophosphamide, vincristine, melphalan, and prednisone (M-2).

RESULTS

The objective responses to idarubicin p.o. in this study are noted in Table 3. One patient was ineligible because of the number of prior chemotherapeutic regimens (five) and because of histological diagnosis (diffuse, poorly differentiated lymphocytic lymphoma). An overall response rate of 58% was observed (95% confidence limits, 46–70%). The duration of remission in CR patients was 8+ months (3+–41+ months) and that in PR patients was 5+ months (2–40+ months). The median number of doses of idarubicin received in this study was 6 (range, 1–17). The median number of doses required to achieve remission was 3 (range, 2–6).

Differential responses to idarubicin were examined for effects of histology, number of prior treatment programs, responses to prior therapy, and stage of malignancy. No statistically significant differences were found among these groups in the response to idarubicin.

The toxicities encountered in this study are noted in Table 4. Hematological toxicity was mild at the initial dose. Twenty-two patients were able to have dose escalations because of the lack of toxicity, usually hematological toxicity, at the initial dose. Myelosuppression was the usual dose-limiting toxicity at higher dose levels of 50 and 55 mg/m². Nausea/vomiting was the dose-limiting toxicity in 18% of the patients with dose escalation.

Nonhematological toxicity was acceptable (Table 4). Nausea/vomiting was seen in 50% of patients and was described as mild in 17 of 22 patients. Mucositis/diarrhea was observed in 20% (9 patients) and was mild in 7 patients and moderate in 2 patients. One case of fulminant fatal hepatitis was observed; the relationship to idarubicin therapy was uncertain.

There was an insignificant change of EF for the patients in this study during the course of therapy; the median initial EF was 0.65 (range, 0.50–0.78) and the median final EF was 0.63 (range, 0.48–0.76). The median dose of idarubicin received in this study was 315 mg/m² (range, 45–765 mg/m²). Four patients developed cardiac effects, all of which were "mild" (EF changes, 0.10–0.15) (9) with cumulative idarubicin doses of 450–630 mg/m². None of these patients developed any cardiac symptoms. No patient developed any acute cardiac symptoms, such as arrhythmias, during the course of therapy.

Table 2 *Characteristics of patients treated with idarubicin*

No. of patients	46
Median age (range)	66 yr (40–85)
Median performance status (range)	1 (0–1)
Median no. of prior chemotherapeutic regimens (range)	1 (1–5[a])
Response to prior therapy	
Refractory	5
Relapsing	41
Histology[b]	
NPDL	12
NM	9
DWDL	24
DPDL	1[a]
Stage	
II B	1
III	8
IV	37

[a] Ineligible.
[b] NPDL, nodular poorly differentiated lymphocytic; NM, nodular mixed; DWDL, diffuse well-differentiated lymphocytic; DPDL, diffuse poorly differentiated lymphocytic.

Table 3 *Response to idarubicin p.o. in non-Hodgkin's lymphoma*

	No. of patients	
No. of eligible patients	45	
Best response[a]		
CR	10	58%
PR	16	
NC	8	
PD	11	

[a] The median duration of response was 6+ months and the range was 2–41+ months. NC, no change; PD, progressive disease.

DISCUSSION

Idarubicin has been the subject of two studies in patients with lymphoma. In one trial with the i.v. preparation, no responses were observed in the 22 patients treated. Of these patients, 16 had non-Hodgkin's disease (2 low-grade lymphoma); all patients had received prior anthracycline (5). In one trial utilizing idarubicin p.o., patients previously treated and previously untreated were included. Of those seven previously treated patients with non-Hodgkin's lymphoma, two patients responded, both of whom had low-grade lymphoma (6). Nonhematological toxicity was mild and the dose-limiting toxicity was hematological in both studies.

In the current trial in 46 previously treated patients with low-

Table 4 *Toxicity of idarubicin*

	Cells/mm³	
Parameter	Median	Range
WBC nadir	4,100	800–83,600
Platelet nadir	147,000	12,000–325,000
Toxicity		No. (%)
Nausea/vomiting		23 (50)
Mucositis/diarrhea		9 (20)
Alopecia		7 (15)
Anorexia		5 (11)
Sepsis		1 (2)
Fatal hepatitis		1 (2)

grade lymphoma, 58% responded to therapy. The results of the present and prior trials in patients with non-Hodgkin's lymphoma (6) suggest significant activity in previously untreated and previously treated patients with low-grade lymphoma. The reported results with i.v. idarubicin suggest cross-resistance of idarubicin with doxorubicin (5). Only four patients in the previously published study of p.o. therapy had received doxorubicin; the response of idarubicin in these patients with prior anthracycline treatment was not delineated.

Oral idarubicin was generally well tolerated, with myelosuppression as the dose-limiting toxicity. The toxicity profile is comparable to that in the previously published study of idarubicin p.o. (6). However, delayed hematological recovery was not observed in this study utilizing a 3-week cycle of therapy. Nausea/vomiting was tolerable and comparable to that in the other phase II study in lymphoma patients (6) but was less than that seen in phase I studies at doses of >40 mg/m^2 (3, 4). This difference may be due to dose fractionation and/or routine medication with antiemetics in this study.

Symptomatic cardiac toxicity was not observed in other studies of lymphoma (5, 6) or seen in the present trial. Ejection fractions were determined periodically in the present study. The overall EF did not change for the entire group. Four patients did have significant changes in EF; all were mild (≥0.10 change) (9) and the patients were asymptomatic.

Idarubicin in oral form is an active drug as a single agent in previously treated patients with low-grade lymphoma. Present and prior studies with idarubicin suggest that this drug could be considered for trial with other active agents in lymphoma patients without prior anthracycline treatment.

REFERENCES

1. Arcamone, F., Bernard, L., Giardino, P., Patelli, B., DiMarco, A., Casazza, A. M., and Pratesi, P. Synthesis and anti-tumor activity of 4-demethoxydaunorubicin, 4-demethoxy-7,9-diepidaunorubicin, and their B anomers. Cancer Treat. Rep., *60:* 829–834, 1976.
2. Giuliani, F. C., Spreafico, F., and Casazza, A. M. Preclinical studies on new anthracyclines: antitumor toxicologic and pharmacologic properties. *In:* H. H. Hansen (ed.), Anthracyclines and Cancer Therapy, pp. 193–207. Amsterdam: Excerpta Medica, 1983.
3. Bonfante, V., Ferrari, L., Villani, F., and Bonadonna, G. Phase I study of 4-demethoxy-daunorubicin. Invest. New Drugs, *1:* 161–168, 1983.
4. Kaplan, S., Sessa, C., Willems, Y., Pacciarini, M. A., Tamassia, V., and Cavalli, F. Phase I trial of 4-demethoxydaunorubicin (idarubicin) with single oral doses. Invest. New Drugs, *2:* 281–286, 1984.
5. Coonley, C. J., Warrell, R. P., Jr., Straus, D. J., and Young, C. W. Clinical evaluation of 4-demethoxydaunorubicin in patients with advanced malignant lymphoma. Cancer Treat. Rep., *67:* 949–950, 1983.
6. Lopez, M., DiLauro, L., and Papaldo, P. Oral idarubicin in non-Hodgkin's lymphoma. Invest. New Drugs, *4:* 263–267, 1986.
7. Krueger, G., Medina, J., Klein, H., Konrads, A., Zach, J., Rister, M., Janik, G., Evers, K., Hirano, T., Kitamura, H., and Bedoya, V. A new working formulation of non-Hodgkin's lymphomas. Cancer (Phila.), *52:* 833–840, 1983.
8. Rappaport, H. Tumours of the hematopoietic system. *In:* Atlas of Tumour Pathology. Washington, DC. Armed Forces Institute of Pathology, 1966.
9. Alexander, J., Dainiak, N., Berger, H., Goldman, L., Johnstone, D., Reduto, L., Duffy, T., Schwartz, P., Goddacalt, A., and Zaret, B. Serial assessment of doxorubicin cardiomyopathy with quantitative radionuclide angiography. N. Engl. J. Med., *300:* 278–283, 1979.