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Good tolerance of weekly oral idarubicin: (4-demethoxydaunorubicin): A phase I study with pharmacology*

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Summary. Idarubicin (4-demethoxydaunorubicin) is an orally active anthracycline. We treated 26 patients with 37 courses of the drug on a schedule of oral administration weekly × 3 followed by a 3-week rest period. The maximum tolerated dose on this schedule was 22.5 mg/m^2 weekly × 3 every 6 weeks, with consistent myelosuppression being the dose-limiting toxicity; other toxicity was minimal. Pharmacologic studies showed a mean alpha half-life of 1.6 ± 0.3 h and a beta half-life of 39 ± 8.4 h for idarubicin. This schedule was well tolerated, with consistent toxicity patterns seen. Pharmacologic studies confirmed prolonged exposure to the drug and its active metabolite. In comparison with other schedules, this one may offer advantages in terms of consistent hematologic toxicity and prolonged exposure to both the parent compound and its active metabolite. Dose intensity was comparable with that on other schedules.

Introduction

The anthracycline antibiotics contribute significantly to anticancer chemotherapy because of their wide spectrum and substantial activity in specific tumors. However, dose-dependent chronic cardiomyopathy and severe vesicant activity on paravenous extravasation are toxicities unique to their use. Anthracycline analog development has been undertaken to overcome these problems. Arcamone and colleagues [1] have synthesized a family of anthracyclines lacking the methoxy group on the D-ring of the 4-ring anthracycline moiety. This lack of the methoxy group increases the lipophilicity of the compound and, hence, its absorption across the gastrointestinal (GI) mucosa [15].

One such molecule is 4-demethoxydaunorubicin (idarubicin; Adria Labs, Columbus, Ohio), which is available as both oral and intravenous preparations for clinical trials. Preclinical activity comparable with that of daunorubicin has been reported against P388, L1210 and Gross' leukemia [15], sarcoma S180 [1], and murine T-cell lymphoma [4]. On the other hand, idarubicin is also less cardiotoxic than doxorubicin or daunorubicin in the rabbit, mouse, and dog when given intravenously [6]. In mice, idarubicin gave higher serum and noncardiac tissue drug levels than the parent compound, daunorubicin. In particular, oral idarubicin provided the most favorable ratio of tumor-to-heart drug concentrations [4]. Pharmacologic studies using the oral formulation in humans on a number of different schedules have been reported. These include three divided doses over 24 h given every 3 weeks [13], weekly [16], daily on 3–5 consecutive days every 3 weeks [12], and one oral dose every 3–4 weeks [3, 11]. Phase II studies have been conducted in most tumors to date, with activity noted against leukemia [5], myeloma [7], and breast cancer [2]. Most studies have not reported cardiac toxicity, probably due to limited numbers of patients receiving a large cumulative dose.

We investigated the weekly administration and pharmacokinetics of oral idarubicin in this phase I study. We chose this schedule because our previous experience with a more intermittent dosing schedule suggested unpredictable myelotoxicity [8]. Furthermore, there is evidence that the weekly administration of anthracyclines lowers the incidence of cardiac toxicity [17], and a weekly schedule could prove to be less cardiotoxic in future, large-scale trials.

Patients and methods

Patients. All patients were accrued from New York University Medical Center and the Bellevue Hospital Medical Center. Eligibility criteria included histological confirmation of a malignant, solid tumor refractory to conventional methods of therapy; recovery from previous surgery or

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Table 1. Patient characteristics

Entered	26
Men	15
Women	11
Performance status (ECOG):	
0	5
1	14
2	7
Median age (range)	62 (36–76) years
Disease:	
Lung cancer	9
Melanoma	6
Colorectal cancer	3
Gastric cancer	2
Pancreas cancer	1
Hepatoma	1
Bladder cancer	1
Sarcoma	1
Prior chemotherapy:	
0	8
1	1
2	6
3	2
Prior radiation	16

radiation therapy an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; pretreatment organ function within the following limits: a granulocyte count of $\geq 1.5 \times 10^9$/l a platelet count of $\geq 100 \times 10^9$/l, serum creatinine levels of <1.5 mg/dl, bilirubin values of <2.0 mg/dl, and alkaline phosphatase values less than twice the upper limit of normal. Patients were excluded if they showed evidence of cardiac disease, if their left ventricular ejection fraction was <50%, or if they had a GI disturbance that would have interfered with drug absorption. All patients were informed of the investigational nature of the study and were required to give written informed consent prior to the initiation of treatment. The protocol was approved by the Institutional Review Boards of New York University and Bellevue Medical Centers.

Pretreatment evaluation included a history and physical examination, routine complete blood and platelet counts with a differential white cell count, a chest X-ray, and a left ventricular ejection-fraction determination by a gated radionuclide heart (MUGA) scan. The toxicity and response criteria were those of the ECOG [14].

Treatment. Idarubicin was supplied as 5- and 10-mg capsules by Adria Laboratories of Columbus, Ohio. Patients were fasted overnight and the drug dose, corrected to the nearest 5 mg, was given p.o. with 200 cm^3 water. Dosing was carried out weekly for 3 weeks, with a 3-week hiatus. Patients were then eligible to be retreated at the same dose if there was no disease progression and no moderated or severe toxicity. The starting dose (10 mg/m^2 weekly) represented about 1/3 of the tolerable dose of idarubicin given as a single intravenous injection. Dose escalation took place as long as no moderate or severe toxicity was documented in three of four patients treated at a given dose level. The dose-limiting toxicity (DLT) was defined as any nonhematologic grade 2 toxicity or a grade 3 myelotoxicity. The maximum tolerated dose (MTD) was defined as that producing dose-limiting toxicity in four of six patients.

Analytical methodology. Idarubicin was measured by HPLC using a modification of the method described by Israel et al. [10]. The HPLC instrumentation consisted of two Waters pumps (M6000A and M45) along with a WISP model 710B autosampler (Waters Associates, Milford, Mass.). The pumps and WISP were controlled by an Axxiom 747 multisystem controller-data system (Cole Scientific, Calabasas, Calif.). For fluorescent detection we used an Applied Bio-systems model 970 fluorescence detector (Ramsey, N. J.). Doxorubicin was used as a recovery standard.

Idarubicin, its metabolites, and the internal standard, doxorubicin (Dox), were extracted from the plasma using a double extraction that followed a modification of the procedure previously described Green [8]. In all, 5 ml blood was obtained in heparinized tubes at 0, 0.5, 1, 2, 4, 6, 8, 12, 18, 24, 30, 36, and 48 h after idarubicin administration and the plasma was separated by centrifugation and frozen at –20° C. To 1 ml thawed plasma, 200 ng Dox internal standard and 0.5 ml 0.05 *M* TRIS-HCl buffer (pH 8.5) was added prior to the organic extraction procedure. The aqueous solution was extracted with 4 ml chloroform : 1-propanol (3 : 1, v/v) by rapid vortexing for 10 s and immediate centrifugation at 4,000 *g* for 10 min in centrifugal separator tubes fitted with a rubber septum (Kontes Glass, Vineland, N. J.). The lower layer was removed with a glass syringe and the aqueous layer, reextracted with an additional 4 ml chloroform : 1-propanol. The collected extracts were either taken under a stream of nitrogen or evaporated to dryness in a Savant Speed-Vac. The extracts were stored dry at –20° C and redissolved in 0.35 ml methanol just prior to analysis by HPLC; 100–200 µl concentrate was injected for analysis. Urine samples were analyzed directly after a 5-min centrifugation at 12,000 *g*; 10–50 µl was injected for analysis.

Chromatography was carried out by gradient elution on a reverse-phase, 5-µm, phenyl, 0.45 × 25-cm analytical column (Phase Separation, Norwalk, Conn.). Mobile phase A consisted of 0.1% ammonium phosphate (adjusted to pH 2.5 with formic acid) and mobile phase B comprised 100% acetonitrile. A linear gradient of 60%A/40%B to 40%A/60%B was developed over a 12-min cycle, followed by a 2-min re-equilibration of the column. The flow rate was 1.5 ml/min. Fluorescent detection used 482 nm excitation and 515 nm emission. Under these conditions, dox, 13-DMDR-ol, and idarubicin eluted with retention times of 5.0, 6.0, and 6.7 min respectively. Using a sensitivity setting of 0.01 µA, idarubicin and its alcohol metabolite could be detected to a lower limit of 0.5 ng/ml; the system was calibrated over the range of 0.5–50 ng/ml.

Pharmacokinetic values were obtained by first using the JANA curve-stripping program to estimate the initial pharmacokinetic parameters prior to modeling using PCNONLIN (Statistical Consultants, Lexington, Ky.). The estimates were used as the initial parameters for a two-compartment oral absorption model. The program used these initial parameters to fit the data to the best curve possible and then applied Lagrangian techniques to reduce the total variance of the key pharmacokinetic values.

Results

A total of 26 patients including 11 women and 15 men were entered in this study and treated with 37 courses (110 doses) of oral idarubicin (Table 1). The median age of the patients was 62 years and their median ECOG performance status was 1. In all, 8 patients had not undergone prior chemotherapy and the other 18 had received 1–3 prior regimens. Of 26 patients, 10 had not been irradiated; 7 had not previously received either chemotherapy or radiation treatment.

The major dose-limiting toxicity in this study was myelosuppression (Table 2). No significant hematologic suppression was seen in 13 patients treated with 10–17.5 mg/m^2 weekly. In the six patients receiving doses of 20 mg/m^2 weekly × 3, minimal leukopenia was seen, with the lowest WBC count being 2,000/mm^3. Of the seven patients treated at 22.5 mg/m^2, one had grade 3 leukopenia (1,700/mm^3) and the final two patients had grade 4 leukopenia, each with 600/mm^2 WBC. Two of these three patients had not previously undergone chemotherapy and the third had only received one prior regimen. The median

Table 2. Hematologic toxicity

Dose (mg/m^2)	Patients (n)	Median WBC nadir and range ($\times 10^3/mm^3$)		Median Plt nadir and range ($\times 10^3/mm^3$)		Cycles (n)
10	4	4.2	(4.0–9.5)	272	(220–316)	$4^1/_3$
15	4	3.7	(1.8–6.5)	298	(136–412)	$7^2/_3$
17.5	5	6.0	(3.0–10.5)	306	(152–378)	$8^1/_3$
20	6	3.6	(2.0–7.4)	355	(230–466)	9
22.5	7	3.3	(0.6–4.7)	167	(71–306)	$7^1/_3$

Plt, platelet

Table 3. Pharmacokinetics of idarubicin and 13-DMDR-ol

Patient	Dose (mg)	K_{OI} (h^{-1})	$t_1/2\alpha$ (h)	$t_1/2\beta$ (h)	AUC ($ng \times h\ ml^{-1}$)
MZ	25	2.3	3.0	66	338
DS	30	0.72	0.87	31	49.6
PC	30	1.5	1.7	77	51.2
MN	30	0.90	2.9	29	13.9
JR	30	0.85	1.6	8.3	212
MS	35	0.44	2.2	15.6	102
TB	40	0.88	0.8	12.3	99
LG	40	0.46	1.5	12.9	237
RA	35	0.42	2.0	29	93
FA	40	0.5	0.76	64	156
HG	40	0.5	0.17	8.1	46
Mean		0.86	1.6	39	
SEM		0.17	0.27	8.4	

Patient	C_{max} DMDR (ng/ml)	T_{max} (h)	C_{max} DMDR-ol (ng/ml)	T_{max} (h)
MZ	9.0	4.3	–	–
DS	8.0	1.2	19	1.5
PC	3.7	2.4	15.1	2.6
MN	5.8	2.3	10.8	3.3
JR	5.8	1.8	–	–
MS	4.8	3.5	15.9	3.5
TB	6.0	6.0	–	–
LG	9.2	4.7	10.8	3.5
RA	8.3	2.5	7.8	2.6
FA	9.7	0.9	–	–
HG	14.7	0.3	–	–
Mean		2.72		2.8
SEM		0.53		0.3

Table 4. Urinary recovery of idarubicin and 13-DMDR-ol

Patient	Dose (mg/m^2)	Dose (mg)	Idarubicin	13-DMDR-ol	Totals
MZ	15	25	0.8%	3.6%	4.4%
DS	17.5	30	0.9%	4.3%	5.2%
PC	17.5	30	0.1%	0.2%	0.3%
MN	20	30	0.9%	6.3%	7.2%
JR	20	30	1.1%	5.1%	6.2%
MS	20	35	0.5%	4.2%	4.7%
TB	20	40	0.6%	2.8%	3.4%
LG	22.5	40	0.8%	4.4%	5.2%
RA	22.5	35	0.3%	1.9%	2.2%
FA	22.5	40	0.4%	7.0%	7.4%
HG	22.5	40	1.1%	1.9%	3.0%
Mean			0.7%	4.1%	4.9%
SEM			0.1%	0.5%	0.6%

13-DMDR-ol, 13-idarubicin-ol

time to the WBC nadir in 21 first cycles was 21 days (range, 9–29 days), with all patients' granulocytopenia resolving by day 35. In all cases WBC counts recovered completely. No thrombocytopenia was seen in 23 patients. Only 2 patients developed grade 1 and one, grade 2 thrombocytopenia, which was associated with the episodes of grade 3 or 4 leukopenia described above. Seven patients receiving two or more courses failed to show evidence of more severe myelosuppression on their subsequent courses, although all of these patients received doses of $\leqslant 20\ mg/m^2$.

Nonhematologic toxicity was minimal. Eight patients had grade 2 nausea and vomiting and six reported nausea alone (grade 1). Vomiting was usually delayed until 6–8 h after drug administration. No patient noted evidence of red material in the vomitus. Seven patients reported mild fatigue and one experienced moderate (grade 2) fatigue. One patient required hospitalization for lower GI bleeding (diverticular) but had a normal platelet count at the time.

No major therapeutic responses were seen. One patient with breast cancer had relief of bone pain and remained on the drug for four cycles before progressing. One patient with lung cancer had a less than partial response as determined by measurements and received three cycles.

Pharmacokinetic studies were conducted on patients at all doses. At the lowest doses of up to 15 mg/m^2, idarubicin levels could not be consistently detected. A total of 11 patients had drug levels that were detectable for up to 48 h, and these data could be modeled (Table 3). Absorption was consistent, with a rate constant of $0.86 \pm 0.17\ h^{-1}$ (mean $\pm$ SEM). The maximal time to peak concentration (T_{max}) was 2.7 ± 0.5 h. The maximal concentration (C_{max}) ranged from 3.7 to 14.7 ng/ml and, over the narrow range investigated, was not dose-related. The AUCs reflected the C_{max} and the prolonged beta half-life ($t_1/2\beta$) of 38.6 ± 8.4 h.

Neither the AUC nor peak concentrations correlated with dose or degree of myelosuppression. In the two patients who developed grade 4 leukopenia, peak concentrations and AUC were 9.2 ng/ml and 237 and 8.3 and 93, respectively. These were not the highest levels seen for either parameter; some patients with higher peak concentration levels and AUCs did not develop hematologic toxicities. We also report the peak concentrations for the active metabolite 13-hydroxy-idarubicin (idarubicin-ol) and the time to peak concentration (Table 3). In all cases, peak idarubicin-ol concentrations were higher than those of the parent compound, ranging from 7.8 to 19.0 ng/ml. Urinary excretion for 11 patients was $0.7\% \pm 0.1\%$ for idarubicin and $4.1\% \pm 0.5\%$ for 13-idarubicin-ol (Table 4).

Discussion

We report a phase I study of weekly oral idarubicin, a compound unique in the clinic as an orally active anthracycline. The drug was given each week for 3 consecutive weeks, the rationale for this schedule being based on the previously reported prolonged half-life of the drug. Furthermore, idarubicin is metabolized to the alcohol, 13-hydroxy-idarubicin-ol, an active antitumor agent. When the drug is given orally, idarubicin-ol plasma levels are found at even higher concentrations and a longer half-life (3–5 days) than those of the parent compound. A weekly schedule would enable a prolonged and nearly continuous exposure to these active antitumor agents.

We found this schedule to be well tolerated by our patients. Nonhematologic toxicity was minimal, with less than one-third of the patients reporting even mild nausea and vomiting, which was relatively delayed as compared with the pharmacokinetics of drug absorption. Myelosuppression was not seen at doses of up to 20 mg/m^2 weekly. At 22.5 mg/m^2, three of seven patients had grade 3 or 4 myelosuppression, including two with WBC nadirs of 600/mm^3; the other patients, however, had no myelosuppression.

Our pharmacokinetic studies are consistent with reports from other investigators [3, 11, 12, 16]. The $t_1/2\alpha$ and $t_1/2\beta$ values were 1.6 ± 0.3 and 38.6 ± 8.4 h, respectively, for idarubicin. This may be compared with values for doxorubicin, which has a $t_1/2\alpha$ of 2–3 h and a terminal half-life of 25–28 h. Absorption was consistent as determined by peak concentration and time to peak concentration. Our metabolite data (Table 3) are also consistent with previously reported results, suggesting AUC ratios for idarubicin-ol: idarubicin of 2:1–3:1 [12, 16]. The oral route also provides an advantage for conversion to 13-idarubicin-ol by first-pass metabolism, as compared with intravenous administration. The weekly oral route can therefore provide truly prolonged exposure to idarubicin and, especially, to its active metabolite.

In this study, we found oral idarubicin given weekly $\times 3$ to be well tolerated and practical. Drug absorption was consistent based on pharmacokinetic studies. Toxicity was mild, with dose-limiting myelosuppression. The median time to the WBC nadir was 21 days, with all patients achieving this nadir by day 28. We found this schedule to be less erratic with regard to myelosuppression than that used in a previous phase II study, i.e., the oral "bolus" schedule of 40 mg/m^2 every 4 weeks [9], during which we noted sporadic, severe myelosuppression. The prolonged half-lives of the parent drug and the metabolite may make this schedule advantageous for diseases with long cycling times against which activity has been shown, such as myeloma and breast cancer, of idarubicin [2, 7]. This drug is also active against leukemia, and weekly low oral doses may be especially useful in myelodysplastic syndromes. We can recommend a phase II dose of 20 mg/m^2 weekly $\times 3$, with some patients tolerating escalations to higher doses. Based on the recovery of WBC counts by days 28–35, the cycles can be safely repeated every 5 weeks, resulting in a dose intensity at least comparable with that achieved on the "bolus" of daily $\times 3$ schedules. This schedule therefore appears to offer advantages in terms of safety, pharmacokinetics, and, possibly, dose intensity.

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