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Phase I Trial of 4-Demethoxydaunorubicin with Single i.v. Doses*

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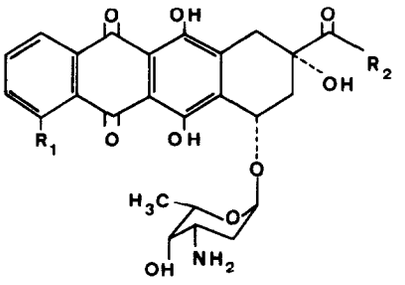
Abstract—*Sixteen adult patients with a variety of solid tumors entered a phase I trial with 4-demethoxydaunorubicin, a new analogue of daunorubicin. The drug was given as a single i.v. dose of* 5–18 mg/m² *repeated every* 3–4 weeks. *Myelosuppression, especially leucopenia, was dose-limiting. Other toxic effects included mild to moderate nausea and vomiting. The maximum tolerated dose for ambulatory treatment was* 18 mg/m², *and* 15 mg/m² *every* 3–4 weeks *is proposed as a starting dose for phase II trials in solid tumors.*

INTRODUCTION

MUCH effort is being continuously devoted to the development of new analogues of conventional chemotherapeutic agents in the search of new compounds with broader antitumor activity and a better therapeutic index. Anthracycline derivatives are being extensively investigated for this purpose.

4-Demethoxydaunorubicin (IMI-30) is a new daunorubicin analogue (Fig. 1) which lacks the methoxy group at the C-4 position in the aglycone [1, 2]. IMI-30 was found to be effective in a variety of experimental murine tumors. In the L1210 and the gross leukemias IMI-30 shows antitumor activity similar to that of daunorubicin at doses 5–8 times lower. IMI-30 is also active by the oral route. At optimal doses, which are about 4 times higher than the optimal i.v. doses, oral IMI-30 achieves the same antitumor activity as the i.v. form and is as effective as i.p. doxorubicin against ascitic P388 leukemia and as i.v. doxorubicin against L1210 leukemia [3, 4]. Initial toxicologic data suggest a better therapeutic index of IMI-30 relative to the parent compound [5], particularly as regards cardiotoxicity.

This clinical phase I trial with 4-demethoxydaunorubicin aimed at defining the maximum tolerated dose (MTD) and the acute toxic effects with an intermittent single i.v. dose schedule. Results of our phase I trial with the oral formulation of IMI-30 will be reported elsewhere (Kaplan *et al.*, in preparation). These studies were undertaken as part of the new drug program of the Early Clinical Trials Group of the EORTC.



	R_1	R_2
ADRIAMYCIN	OCH_3	CH_2OH
DAUNORUBICIN	OCH_3	CH_3
CARMINOMYCIN	OH	CH_3
4-DEMETHOXYDAUNORUBICIN	H	CH_3

Fig. 1.

MATERIALS AND METHODS

All patients selected for this trial had histologically confirmed solid malignancies no longer suitable for conventional therapy. They had completely recovered from major toxic effects induced by prior treatment. All patients had white blood cell counts (WBC) of at least 4000/mm³, platelet counts of 100,000/mm³ or more, and maximum serum creatinine and bilirubin levels of 1.5 mg%. None of the patients had cardiac disease. Expected survival upon entry into the trial was longer than 6 weeks. Three complete blood cell counts and one SMA 12 chemistry panel

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were scheduled per week. Serial ECGs were performed before drug administration as well as 1 hr, 24 hr and 1 week thereafter. In patients with measurable disease, tumor response was assessed according to conventional response criteria [6].

The drug was supplied by Farmitalia-Carlo Erba S.p.A., Milan, Italy, in vials containing 5 mg of 4-demethoxydaunorubicin as a dry substance. It was reconstituted with 5 ml of saline. The drug was administered i.v. for 3–5 min.

Comparing toxicologic data of daunorubicin and IMI-30 in animals, we fixed the starting dose at 5 mg/m^2 i.v., which corresponds roughly to 1/5 of the LD_{10} (mg/m^2) in dogs. A modified Fibonacci escalation scheme was used. Sixteen patients with far-advanced malignancies entered the study between November 1980 and April 1981. All but one patient had been previously treated with various chemotherapeutic regimens. None had received prior anthracycline therapy. There were 10 men and 6 women. Age ranged between 42 and 75 yr, with a median of 60 yr. The median performance status was 80 on the Karnofsky scale (range 40–90). Eight patients had lung cancer, five had colorectal cancer, two had tumor of the head and neck and one patient had synoviosarcoma. Two to seven patients and one to two courses per patient were evaluated at each dose level (see Table 1). Courses were repeated every 3 weeks or upon recovery of toxic effects. None of the patients were re-treated at higher doses. Pharmacokinetic studies were performed in 4 patients. IMI-30 and its reduced metabolite were measured in plasma and urine by means of a high-pressure liquid chromatography method described by Moro *et al.* [7] for other anthracycline analogues.

RESULTS

The dose-limiting factor was clearly myelosuppression. Fourteen patients were completely evaluable for hematologic, gastrointestinal and acute cardiac toxicity. One patient treated at the first dose level died of disease progression on day 9 after treatment: another patient treated with 18 mg/m^2 expired on day 16 with agranulocytosis and septicemia.

No significant hematologic toxicity was observed among patients treated with 5 mg/m^2 and 10 mg/m^2 (Table 1). Myelosuppression was observed in all 7 patients treated with 15 mg/m^2. Four of these had liver metastases and exhibited, upon entry into the trial, increased serum levels of alkaline phosphatase to less than twice the upper value of the normal range, with no abnormalities in bilirubin GOT and GPT levels.

At least three of these 4 patients had had very extensive prior treatment and were known for reduced bone marrow tolerance to cytotoxic drugs. Among these four patients the median WBC nadir was 1.2×10^3/mm^3 (range 0.6–2.0 $\times 10^3$/mm^3), the median granulocyte count was 0.2×10^3/mm^3 (range 0.06–0.8 $\times 10^3$/mm^3) and the median platelet nadir was 60.0×10^3/mm^3 (range 42.0–100.0 $\times 10^3$/mm^3). Three additional patients with normal liver function tests were treated with 15 mg/m^2 and had shown fair tolerance to previous chemotherapy. The three patients had a median WBC nadir of 2.4×10^3/mm^3 (range 1.9–3.6 $\times 10^3$/mm^3), a median granulocyte count of 1.4×10^3/mm^3 (range 1.2–2.1 $\times 10^3$/mm^3) and a median platelet nadir of 120.0×10^3/mm^3 (range 90.0–170.0 $\times 10^3$/mm^3). Among all patients entered at the dose level of 15 mg/m^2, the median day of nadir was day 9 (range 7–11) for WBC and day 13 (range 9–14) for platelets, whereas the corresponding median days of recovery were day 23 (range 21–28) and day 24 (range 18–30) respectively.

With 18 mg/m^2 one patient had no prior treatment and four others had shown fair hematologic tolerance to prior chemotherapy. Only 2 of these 5 patients had known liver metastases with minimal increase of alkaline phosphatase. At this level the median nadir of WBC was 1.0×10^3/mm^3 (range 0.1–2.1 $\times 10^3$/mm^3) and the median granulocyte count was 0.4×10^3/mm^3 (range 0–1.0 $\times 10^3$/mm^3). The median platelet nadir was 65.0×10^3/mm^3 (range 28–116 $\times 10^3$/mm^3). The median day of nadir was day 9 (range 8–15) for WBC and day 13 (range 10–15) for platelets. The median occurrence or recovery was observed for WBC on day 24 (18–30) and on day 28 (24–30) for platelets. All 5 patients showed an important decrease in hemoglobin levels, with a median value of 3 g% (range 1.8–3.9 g%). One toxic death occurred on day 16 in a 75-yr-old male with squamous cell carcinoma of the lung. On day 14 he developed Gram-negative septicemia while WBC were 0.1×10^3/mm^3. Of the 6 patients who received 2 courses of treatment with 15 or 18 mg/m^2 none showed different patterns of myelosuppression between the 2 courses. At almost all treatment levels a significant decrease in the median hemoglobin value, ranging from 1.7 to 3.0 g%, was observed (Table 1). There was no clear evidence of hemorrhage or hemolysis in any of these patients.

Non-hematologic toxic effects were mostly negligible (Table 2). Three patients had nausea and one had moderate vomiting for 3 days. Nausea occurred generally 3–4 hr after drug administration. No phlebitis or extravasation was observed. Alopecia was noted in the single previously untreated patient; all other patients had hair loss from prior therapy upon entry in the study. No stomatitis was encountered. None of the

Table 1. *Hematologic toxicity*

Dose mg/m²	No. of patients	Total No. of courses	Median nadir × 10³/mm³ (range) WBC	Granulocytes	Platelets	Median decrease of Hb, G%
5	2*	2	7.5	—	139	1.8
10	2	2	3.75 (3.5–4.0)	—	220 (190–250)	—
15	4†	6	1.2 (0.6–2.0)	0.2 (0.06–0.8)	60 (42–100)	2.0 (0.6–5)
	3‡	5	2.4 (1.9–3.6)	1.4 (1.2–2.1)	120 (90–170)	1.7 (1.6–3.0)
18	5	7	1.0 (0.1–2.1)	0.4 (0–1.0)	65 (28–116)	3.0 (1.8–3.9)

*One patient only partially evaluable (early death).
†Patients with liver function impairment.
‡Patients with normal liver function.

Table 2. *Non-hematologic toxicity*

Dose mg/m²	No. of patients	Nausea	Vomiting	Stomatitis	ECG
5	2*	0	0	0	—
10	2	2	0	0	—
15	7	1	0	0	0/3
18	5	0	1	0	0/3

*One patient only partially evaluable (early death).

patients showed electrocardiographic changes. No objective tumor responses were observed in this trial.

Only preliminary pharmacokinetic data are currently available (Fig. 2). Plasma levels of IMI-30 and of its main metabolite 13-hydroxy-4-demethoxydaunorubicin (13-OH-IMI-30) were obtained in 4 patients after the administration of 18 mg/m². The plasma disappearance curve of the parent compound seems to follow a triphasic pattern with $t_{\frac{1}{2}}\alpha$ of about 30 min and $t_{\frac{1}{2}}\beta$ of 6 hr. Data are still insufficient to calculate the terminal half-life. Further studies with determinations for up to 72 hr after drug administrations are ongoing in other patients.

13-OH-IMI-30 is already measurable after 15 min in the plasma; its concentration steadily increases until the 4th hour and plateaus thereafter up to the last sampling time. Plasma levels of 13-OH-IMI-30 become higher than those of IMI-30 between the 4th and the 5th hours.

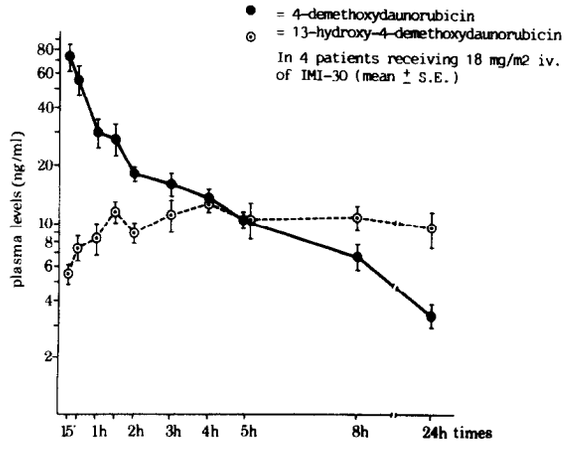

Fig. 2.

The cumulative 24-hr urinary excretion of the unchanged species is about 5% of the administered dose, while an additional 8% is recovered as 13-OH-IMI-30.

DISCUSSION

Anthracyclines presently have a major role in the treatment of a large variety of malignant diseases [8, 9]. Nevertheless, the long-term use of these drugs is limited because of their cumulative cardiac toxicity. The acute toxicity also remains troublesome for many patients. These facts have resulted in a continuous search for analogues having a broader spectrum of activity and a higher therapeutic index.

4-Demethoxydaunorubicin is a new analogue of daunorubicin which showed definite antitumor activity in experimental animal tumors. Early toxicologic data suggest reduced cardiotoxicity as compared to doxorubicin and daunorubicin [5]. The potential for reduced cardiotoxicity was the main reason that prompted the clinical evaluation of this new analogue.

The results of our phase I trial with the i.v. formulation show that hematologic toxicity is dose-limiting. In patients with fair tolerance to chemotherapy and normal liver function 18 mg/m² was found to be the maximum tolerated dose. However, similar hematologic toxicity was found with 15 mg/m² in four patients with liver function impairment and a history of poor tolerance to chemotherapy. A well-known correlation has been demonstrated between hematologic toxicity and liver function in patients treated with other anthracyclines. For patients without liver or bone marrow im-

pairment 15 mg/m² seems to represent a safe starting dose for phase II trials.

Compared to doxorubicin and daunorubicin, 4-demethoxydaunorubicin has, however, a slower recovery of the blood values and possibly also a somewhat more pronounced thrombocytopenia. Therefore, for most patients with solid tumors a single dose every 4 weeks is more suitable than one every 3 weeks. A surprising finding was an important decrease in the median level of hemoglobin without clinical evidence of hemorrhage or hemolysis. Further investigations of these observations are warranted.

The gastrointestinal toxicity observed in this trial appears to be less pronounced than the one that is usually reported with daunorubicin. No cardiotoxicity was detected, but studies on the cumulative cardiotoxicity of this compound remain to be performed. Higher potency relative to daunorubicin, dose-limiting leucopenia with a relatively steep dose–response relationship and minor non-hematologic toxic effects are reminiscent of findings in the phase I trial of carminomycin [10], which is closely related structurally to demethoxydaunorubicin (Fig. 1).

Based on preliminary pharmacokinetic studies, the disappearance curve of IMI-30 seems to fit a triphasic pattern, with a rapid initial decline up to the second hour and a final slow fall in plasma levels beginning after 8 hr. A comparison with daunorubicin is only possible with the results reported by Andersson *et al.* [11] since, to our knowledge, all other available data on daunorubicin pharmacokinetics were obtained through analytical procedures scarcely comparable with our method.

Since Andersson *et al.* [11] administered daunorubicin as a slow i.v. infusion over a period of 45 min–4 hr, only a qualitative comparison between the two drugs is possible.

The most relevant observation is that the behavior of 13-dihydro-derivatives of both drugs is very similar. In fact, plasma levels, once peak level is reached, are higher and the elimination rate is slower for the 13-dihydro-derivative than for the unchanged drug.

In conclusion, we suggest that 18 mg/m² is the maximum tolerated dose for this drug given i.v. in the therapy of solid tumors. Using the same formulation, 15 mg/m² can be proposed as a safe starting dose for phase II trials in patients with normal liver function and fair hematologic tolerance to chemotherapy. The phase I trial with the oral formulation has also been completed and results will be available shortly.

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