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Phase I Clinical Evaluation of Oral and Intravenous 4-Demethoxydaunorubicin*

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Abstract—*Thirteen patients were treated with both the oral and intravenous preparations of 4-demethoxydaunorubicin (DMDR). The drug was well tolerated in both forms. Neutropenia was the dose-limiting side-effect. Approximately 30% of the compound was absorbed when given orally. The maximum tolerated dose was* 12.5 mg/m² *intravenously or* 50 mg/m² (10 mg/m² *q d* × 5) *orally, given every* 21–28 days.

INTRODUCTION

4-DEMETHOXYDAUNORUBICIN (DMDR) is an analog of daunorubicin in which the methoxyl group from the aglycone has been substituted with a hydrogen (Fig. 1). Preclinical screening activity was seen against P-388 and L1210 leukemias and sarcoma 180. DMDR also showed activity when given orally. Animals had measurable drug levels for 3 hr after oral administration and the compound was still detectable after 24 hr [1].

Animal toxicity was similar to that of other anthracyclines; however, cardiac toxicity appears to be less than with doxorubicin. Cardiac lesions in rats were less severe with chronic administration of DMDR. In the New Zealand rabbit the mean cumulative cardiotoxic dose was 290 mg/m², compared to 162 mg/m² for doxorubicin. Even at lethal doses, oral administration of DMDR caused no myocardial lesions in beagles [1].

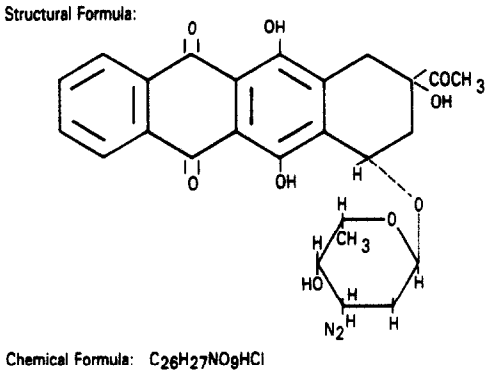
Because of theoretically less cardiac toxicity and the convenience of oral administration, we initiated a phase I trial of demethoxydaunorubicin.

MATERIALS AND METHODS

DMDR was supplied by Farmitalia Carlo Erba. The parenteral form was in 5-mg vials and given in 50 ml of D_5W over 30 min. The oral preparation was in 5- and 10-mg capsules. The total oral dose was given once daily, divided over 5 days. Both intravenous and oral treatments were administered in the morning. If nausea or vomiting developed, an oral antiemetic was given 1 hr prior to oral DMDR. Therapy was repeated every 21 days upon recovery from myelosuppression and other toxicities.

One purpose of the study was to compare the subjective tolerance and pharmacology of the oral and parenteral forms of the compound. Therefore patients initially received one form of therapy and then were switched to the alternate route on the next course. Pharmacology studies were carried out in both courses. Patients were then continued on oral administration of the drug.

Eligibility requirements included histological



Chemical Formula: $C_{26}H_{27}NO_9HCl$

Molecular Weight: 533.97

Fig. 1. 4-Demethoxydaunorubicin (DMDR).

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confirmation of malignancy, failure of standard therapy and proper informed consent. In addition, all patients had a Zubrod performance status of ≤3, adequate hematologic status (granulocytes ≥2000 cells/mm³ and platelet count of ≥100,000 cells/mm³), bilirubin level of ≤1.0 mg/dl and creatinine level of ≤1.5 mg/dl. Patients with a history of significant cardiovascular disease were excluded from the study. Patients with a history of anthracycline exposure within the past year were ineligible. Also, those patients with gastrointestinal findings that would interfere with absorption of the drug were not treated. Patients were monitored with weekly complete blood counts and clinical chemistries. An electrocardiogram and nuclear medicine cardiac ejection fraction was done prior to therapy. The electrocardiogram was repeated prior to each course. The nuclear medicine ejection fraction study was repeated every four courses. Therapy was discontinued for unacceptable toxicity or progression of malignancy despite an adequate drug dosage.

Table 1. Patient characteristics

Total No. evaluable:	12
No. inevaluable:	1 (elevated bilirubin)
Age (yr):	
Median	58
Range	30-79
Performance status (Zubrod scale)	
0	1 (8%)
1	6 (6%)
2	4 (33%)
3	1 (8%)
Sex	
Male	3 (25%)
Female	9 (75%)
Tumor type	
Cervical	4
Ovarian	3
Colon	2
Renal	1
Lymphoma	1
Choriocarcinoma	1
Previous chemotherapy (No. of regimens)	
1	1 (8%)
2	6 (50%)
≥3	5 (42%)

RESULTS

There were 13 patients treated (Table 1). One was not evaluable because of an elevated bilirubin level at the beginning of therapy. Most patients had received one or two other chemotherapy regimens prior to DMDR, and had received prior pelvic radiotherapy. No complete or partial responses were seen in this population. One patient with ovarian cancer had a decrease in the size of liver metastases as seen by computerized tomography.

Myelosuppressive toxicity

Leukopenia was the dose-limiting toxicity in both intravenous and oral forms. The intravenous dose of 12.5 mg/m² every 3 weeks was the maximum tolerated dose (Table 2). This produced a median granulocytopenia of 0.8×10^3 cells/mm³. The median time to nadir was day 15 (range, days 13-23). Recovery to greater than 1.5×10^3 cells/mm³ occurred on day 24 (range, days 21-26).

The oral dose at 10 mg/m² daily for 5 days resulted in a median granulocytopenia of 1.4×10^3/mm³. Time to neutropenia was 21 days (range, days 6-22). Recovery was at day 28, with a range of days 21-34. One patient with extensive lymphoma who was treated at 10 mg/m² daily for 6 days had late and prolonged granulocytopenia (Table 3).

Thrombocytopenia was not a significant problem with either oral or intravenous forms of the drug. No patient required platelet transfusions. There were two courses that caused platelet counts of <50,000 cells/mm³. One was attributed to concurrent use of mitomycin C for control of hypercalcemia.

Non-myelosuppressive toxicity (Table 4)

Nausea and vomiting were infrequent and mild with both the oral and intravenous preparations. One patient developed total alopecia, but most patients were not evaluable for this side-effect.

Table 2. Hematologic toxicity (intravenous)

Dose (mg/m²)	No. of patients	No. of courses	Granulocytes ($\times 10^3$/mm³) Median (range)	Platelets ($\times 10^3$/mm³) Median
10	5	5	1.8 (1.0-1.9)	219
12.5	6	7	0.8 (0.1-1.8)	153

Table 3. Hematologic toxicity (oral)

Dose (mg/m²)	No. of patients	No. of courses	Granulocytes (×10³/mm³) Median (range)	Platelets (×10³/mm³) Median
10 q d × 4	4	4	1.8 (0.5–3.1)	136
10 q d × 5	7	9	1.4 (0.004–2.8)	198
10 q d × 6	1	1	0.9	218

Table 4. Phase I 4-demethoxydaunorubicin (DMDR): non-myelosuppressive toxicity of 26 evaluable courses (range 1–5 per patient)

Nausea (mild)	4 (15%)
Vomiting (mild)	2 (8%) (1 p.o., 1 i.v.)
Alopecia	1 (4%)
Distaste	1 (4%)
Diarrhea	1 (4%)
Extravasation	2 (8%)

Diarrhea of a mild nature occurred in another patient. Two patients developed minimal extravasation of the intravenous compound with a typical anthracycline reaction, but no skin graft was required. No acute cardiovascular toxicity was observed.

Pharmacology

The methodology and detailed clinical pharmacologic data will be reported separately [2; Lu *et al.*, manuscript in preparation]. The drug and its metabolites were quantified by high-performance liquid chromatography and fluorometry. When given intravenously, DMDR had a biphasic plasma clearance with a mean terminal half-life of 16.6 ± 2.2 hr. The volume of distribution was 59.5 + 16.0 l/kg, and total clearance was 2.1 ± 0.5 l/kg/hr. Approximately 5.1 ± 1.1% of the dose was recovered in the urine. When given orally, the half-life was 23.7 hr and peak plasmic concentration was reached in 1 hr. Urinary excretion of the drug was 1.0 ± 0.2% at 24 hr. The gastrointestinal absorption of the compound was 30% of the administered dose. The major metabolite, probably daunorubicinol, had a plasma half-life of 54.6 ± 1.5 and 38 ± 6.5 hr on intravenous and oral administration, respectively. The urinary excretion of the metabolite at 24 hr was 9.3 ± 2.6 and 5.4 ± 1.5%, respectively.

DISCUSSION

The recommended dose of DMDR is 12.5 mg/m² intravenously or 10 mg/m² orally each day for 5 days. The drug may be given every 21–28 days.

There are minimal gastrointestinal side-effects when DMDR is given by divided oral doses. This is in contrast to the study of Bonfante *et al.* [3], where vomiting occurred in over two-thirds and diarrhea in one-third of the patients. The total dose was given in a single day at 60 mg/m². The minor gastrointestinal toxicity encountered in our study may have improved absorption and accounted for the slightly lower oral dose of 50 mg/m². The intravenous dose of 12.5 mg/m² had been recommended earlier by Berman *et al.* [4] and confirmed in a phase II study of DMDr's activity in lymphoma by Coonley *et al.* [5].

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