Phase I and Clinical Pharmacology Studies of Intravenous and Oral Administration of 4-Demethoxydaunorubicin in Patients with Advanced Cancer

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ABSTRACT

4-Demethoxydaunorubicin (4-DMDR), an anthracycline analogue available in i.v. and p.o. form, has shown significant antitumor activity in murine tumor models while producing less cardiac toxicity than doxorubicin at equimyelotoxic doses. Phase I and clinical pharmacology studies of the i.v. and p.o. preparation were performed. With i.v. 4-DMDR, consistent myelosuppression was observed at a dose of 15 mg/sq m at a median Day 15; mild nausea and vomiting were observed in 9% of all treatment courses. In patients given p.o. 4-DMDR, myelosuppression occurred at median Day 14 in 10 of 12 patients given 50 mg/sq m. Nausea and vomiting occurred in 25% of all treatment courses, and dividing the dose over 3 days did not decrease the incidence. Alopecia occurred in 13% of evaluable patients treated with the i.v. preparation and 30% of evaluable patients treated p.o. No stomatitis was observed with either preparation, and no patient developed clinical signs of congestive heart failure. Pharmacokinetic studies were performed with both preparations and revealed prolonged plasma levels of the 13-hydroxy metabolite 4-DMDR-ol. The suggested starting dose for Phase II studies is 12.5 mg/sq m given every 21 days for i.v. 4-DMDR with dose escalation by 2.5 mg/sq m in the absence of myelotoxicity. For p.o. 4-DMDR, the suggested starting dose is 40 mg/sq m given every 21 days with escalation by 10 mg/sq m if no myelotoxicity is observed.

INTRODUCTION

The anthracyclines constitute an important class of antitumor agents. Daunorubicin is probably the most active single agent in the treatment of acute leukemia (11, 20); doxorubicin has a broad spectrum of activity and is useful in a variety of solid tumors (4). The clinical use of the anthracyclines, however, is impeded by the cardiotoxic properties of these compounds; investigators have devoted much effort in recent years in attempts to separate the therapeutic activity from the cardiac toxicity.

One promising approach is the synthesis of analogues. 4-DMDR* is a recent product of the drug development program of Farmitalia Carlo Erba; it differs from its parent compound in the substitution of the C-4 methoxy group with a hydrogen atom (Chart 1). 4-DMDR is more active than daunorubicin in inhibiting RNA synthesis and in inhibiting mouse fibroblast proliferation (13). In the murine leukemia models L1210 and P388, 4-DMDR administered i.v. proved markedly more potent than daunorubicin; the drug was also more active against Gross leukemia than either daunorubicin or doxorubicin (8). Among the solid tumors, 4-DMDR proved active against the solid and ascitic Sarcoma 180 line (2). Unlike daunorubicin or doxorubicin, 4-DMDR has shown activity when administered p.o. in the L1210 (8), Gross leukemia (8), ascitic P388 leukemia (8), and solid Sarcoma 180 (12) models.

Chronic toxicity tests carried out in mice, dogs, and rabbits have shown 4-DMDR to have a significantly reduced cardiotoxic index when compared to daunorubicin or doxorubicin. In dogs treated i.v. for 3 consecutive days/week for 13 weeks at doses 100% lethal to the animals, no myocardial lesions were found (13). This was confirmed by similar data using rabbits (14). In mice, the therapeutic ratios (i.e., the comparative drug doses to produce cardiac toxicity divided by the dosage to produce tumor regression) were doxorubicin, 0.7; daunorubicin, 1.1; and 4-DMDR, 3.1 (7).

Because of the potential clinical advantages of an active p.o. anthracycline with reduced cardiotoxicity, we performed a dose-finding study of both the parenteral and the p.o. formulation of 4-DMDR in patients with advanced cancer. This communication provides the results of that evaluation.

MATERIALS AND METHODS

All patients had a histologically or cytologically confirmed diagnosis of cancer. In all cases, the disease was refractory to standard treatment or was without treatment of established efficacy. Eligibility requirements included a performance status of at least 50% (Karnofsky scale), a life expectancy of at least 8 weeks, a WBC count ≥ 4000/cu mm, a platelet count ≥ 100,000/cu mm, a serum bilirubin < 1.5 mg/dl, and normal serum creatinine (<1.5 mg/dl). No chemotherapy or radiotherapy had been given for at least 4 weeks prior to study entry. Patients with a history of active cardiac disease, prior doxorubicin therapy in excess of 200 mg/sq m, or prior radiotherapy of more than 4000 rads to the mediastinum were excluded; however, one patient who had received 320 mg/sq m of doxorubicin was inadvertently included in this study.

Base-line studies included a complete history and physical examination, chest X-ray, 12-lead electrocardiogram, complete blood count with differential, and automated biochemical screening profile. Pertinent radionuclide scans or computerized tomography were obtained when clinically indicated.

The first few patients in both the i.v. and p.o. study had therapy instituted in the hospital; drug administration was then continued in the outpatient department. The initial dose of the i.v. preparation of 4-DMDR was 5 mg/sq m given every 21 days. Dose escalation was permitted in the individual patient if no objective toxicity was seen within 3 weeks of the initial dose. Dose escalation was 5 mg/sq m for the initial increment and 2.5 mg/sq m thereafter until significant myelosuppression (WBC <

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1 Supported in part by NIH Grant CA 05826 and by a grant from Farmitalia Carlo Erba.
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3 Current address: Cancer Chemotherapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Md. 20020.
4 The abbreviations used are: 4-DMDR, 4-demethoxydaunorubicin; 4-DMDR-ol, 13-hydroxy-4-demethoxydaunorubicin.
5 Received April 15, 1983; accepted August 25, 1983.
RESULTS

Clinical Effects of i.v. 4-DMDR. Twenty-three patients were entered into this part of the study. Twenty-two received adequate and evaluable trials: one patient died within 1 week of rapidly progressive lymphoma. Details of the patient characteristics are provided in Table 1.

Table 2 outlines the dose levels, the number of patients at each level, the total number of treatment courses, and the observed hematological toxicity. Myelosuppression was dose-related, with leukopenia exceeding thrombocytopenia. WBC count nadirs were reached at a median of Day 15 (range, 9 to 20 days). The leukocyte counts returned to normal by Day 21 in all but one patient whose counts were normal by Day 28. Table 3 shows the extent of myelosuppression as a function of the initial dose only; comparison with Table 2 reveals no evidence of cumulative bone marrow toxicity.

Mild nausea and vomiting occurred in 3 of 34 treatment courses (9%), and 1+ alopecia occurred in 2 of 15 patients (13%) who had scalp hair at the beginning of the trial. No stomatitis or diarrhea was reported, and no biochemical evidence of either hepatic or renal toxicity was seen. No patient developed acute cardiac injury, cardiomegaly, or clinical evidence of congestive heart failure; cumulative doses ranged from 5 to 45 mg/sq m; median dose, 20 mg/sq m. One patient developed perivascular hives proximal to the i.v. injection site during drug infusion and was given diphenhydramine with prompt resolution. The rest of the dose was administered with no further problems.

Eleven patients had objectively measurable disease at the start of therapy. No responses were seen among 3 patients with breast cancer, 2 with lung cancer, one with colon cancer, one with ovarian cancer, one with renal cell carcinoma, 2 with melanoma, and one with cancer of the head and neck region.

Clinical Effects of p.o. 4-DMDR. Thirty-two patients received the p.o. formulation of the drug. Thirty received adequate and evaluable trials; one patient with a rapidly growing sarcoma developed brain metastases shortly after his first course, was hospitalized elsewhere, and was lost to follow-up. A second patient with extensive melanoma died suddenly 10 days after receiving the first dose; she had been clinically stable when seen in the clinic on Day 9 and had no history of heart disease.

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Hematological toxicity of initial dose of 4-DMDR given i.v.

Patients entered

<table>
<thead>
<tr>
<th>Dose level (mg/sq m)</th>
<th>Total (evaluable)</th>
<th>WBC nadir&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Median (range)</th>
<th>Median (range)</th>
<th>Maximal decrease in hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5 (4)</td>
<td>4.9 (4.6–5.6)</td>
<td>315 (182–437)</td>
<td>1.3 (0.8–3.9)</td>
<td>2.0 (0.8–5.3)</td>
</tr>
<tr>
<td>10</td>
<td>7 (7)</td>
<td>3.5 (1.8–7.6)</td>
<td>170 (84–528)</td>
<td>1.0 (0.8–3.9)</td>
<td>2.0 (0.8–5.3)</td>
</tr>
<tr>
<td>12.5</td>
<td>6 (5)</td>
<td>2.4 (0.3–3.5)</td>
<td>178 (85–308)</td>
<td>2.0 (0.8–4.3)</td>
<td>2.0 (0.8–5.3)</td>
</tr>
<tr>
<td>15</td>
<td>6 (6)</td>
<td>2.0 (0.6–3.6)</td>
<td>164 (100–284)</td>
<td>2.0 (0.8–5.3)</td>
<td>2.0 (0.8–5.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup> WBC-leukocyte count x 10<sup>9</sup>/cu mm.

Table 3 shows the drug dose levels, the number of patients entered at each dose level, the total number of evaluable courses, and the observed hematological toxicity. As with i.v. administration, p.o. dosing resulted in dose-dependent leukopenia with median WBC count nadir at Day 14 (range, 10 to 17 days). However, as noted in Table 4, the range of WBC count nadirs showed considerable variability, probably indicating erratic absorption of the p.o. preparation. Myelosuppression at a dose of 50 mg/sq m was seen in 10 of 12 patients; only one patient was escalated to 60 mg/sq m. At this dose, his lowest WBC was 4100/cu mm on Day 11 but, because of rapid progression of tumor, no further therapy with 4-DMDR was attempted. As with the i.v. preparation, no cumulative hematological effect was noted.

Significantly more nausea and vomiting were reported with the p.o. preparation than with the i.v. administration. To determine whether dividing the dose of p.o. 4-DMDR had any effect on the pattern of toxicity, 5 patients were treated at initial doses of 50 mg/sq m, the highest dose level tested, with the dose divided as evenly as possible over 3 consecutive days. Dividing did not alter the median WBC nadir (Table 4) or the frequency of nausea or vomiting. Vomiting after both the single and divided dose usually occurred within 2 hr of administration. (One patient who vomited and saw capsular remains in the vomitus had a WBC nadir of 2100/cu mm 15 days after a dose of 40 mg/sq m; this observation is consistent with fairly rapid absorption.) Three patients had transient diarrhea: one, at a dose of 10 mg/sq m, and 2, at a dose of 50 mg/sq m. Five of the 15 patients (33%) beginning the study with scalp hair developed alopecia. No stomatitis or renal or hepatic toxicity was noted.

One 41-year-old female with a cutaneous T-cell lymphoma who had been treated previously with doxorubicin (total dose, 320 mg/sq m) developed atypical chest pain 8 days after a second dose of p.o. 4-DMDR of 40 mg/sq m. Multiple electro-
Hematological toxicity of 4-DMDR given p.o. All evaluable treatment courses were included in the nadir calculations.

<table>
<thead>
<tr>
<th>Dose level (mg/sq m)</th>
<th>Total no. of treatment courses evaluable</th>
<th>WBC nadir&lt;sup&gt;a&lt;/sup&gt; (Median, range)</th>
<th>Platelet nadir&lt;sup&gt;b&lt;/sup&gt; (Median, range)</th>
<th>Maximal decrease in hemoglobin (Median, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>3</td>
<td>6.0 (5.7-8.6)</td>
<td>219 (190-475)</td>
<td>0.7 (1.9-3.1)</td>
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<tr>
<td>20</td>
<td>3</td>
<td>4.7 (3.7-11.8)</td>
<td>265 (153-565)</td>
<td>1.5 (1.1-3.3)</td>
</tr>
<tr>
<td>30</td>
<td>7 (7)</td>
<td>4.8 (2.0-11.4)</td>
<td>265 (132-556)</td>
<td>1.2 (0.1-4.2)</td>
</tr>
<tr>
<td>40</td>
<td>8 (6)</td>
<td>3.5 (0.8-9.6)</td>
<td>190 (38-370)</td>
<td>1.2 (0.2-3.6)</td>
</tr>
<tr>
<td>50 (single dose)</td>
<td>6</td>
<td>2.2 (0.1-7.5)</td>
<td>165 (10-217)</td>
<td>1.9 (0.7-3.6)</td>
</tr>
<tr>
<td>50 (divided dose)</td>
<td>5 (5)</td>
<td>2.3 (0.6-9.5)</td>
<td>195 (66-555)</td>
<td>1.2 (0.7-4.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup> WBC-leukocyte count × 10⁹/cu mm.

<sup>b</sup> Platelet count × 10⁹/cu mm.

cardiograms during episodes of chest pain showed no change from her base-line tracing, and a chest X-ray, cardiac echocardiogram, and lung scan were all normal. A radionuclide ventriculogram showed normal left ventricular wall motion both at rest and during exercise; her normal resting ejection fraction rose appropriately with stress. We felt that the chest pain was not of cardiac origin, but she was not retreated with 4-DMDR because of rapid progression of her disease.

Sixteen patients had objectively measurable disease at the start of treatment; no objective regression was observed in any of the patients given the p.o. preparation. However, one patient with metastatic adenocarcinoma of the lung had stable disease for 7 months and 2 patients, one with epidermoid lung carcinoma and one with epidermoid carcinoma of unknown origin, had stable disease for 3.5 months.

Three patients, all of whom had had extensive chemotherapy before beginning 4-DMDR, were admitted to the hospital with nadir sepsis. All 3 patients survived the episodes of nadir sepsis, and WBC counts returned to normal on Days 17, 19, and 22.

**Pharmacological Studies.** The sequential levels of 4-DMDR and 4-DMDR-ol, in the plasma of 3 patients who received 4-DMDR 12.5 mg/sq m i.v., are shown in Charts 3 and 4. Two of the patients demonstrated triphasic decay curves; the mean t₁/₂ for the 3 patients was 10.5 hr. The mean areas under the curve for 4-DMDR and 4-DMDR-ol were 204.3 and 344.4 µg/hr/liter. Pharmacokinetics of 4-DMDR and 4-DMDR-ol in the plasma of a patient receiving 4-DMDR at 50 mg/sq m p.o. are shown in Chart 5. The t₁/₂ of 4-DMDR in this patient was 9.8 hr. Mean areas under the curve for 4-DMDR and 4-DMDR-ol in 2 patients receiving 50 mg/sq m p.o. were 234.2 and 746.1 µg/hr/liter. 4-DMDR-ol was the only drug metabolite we detected in plasma.

**DISCUSSION**

The principal goal of analogue development is to obtain new drugs with both an improved therapeutic index and a broader spectrum of clinical activity. 4-DMDR is an attractive candidate for further clinical trials because of its favorable antitumor potency:cardiotoxicity ratio, its p.o. bioavailability, and the decreased incidence of nonhematological toxicity. The issues of therapeutic efficacy and chronic cardiotoxicity can only be rigorously addressed in disease-oriented Phase II and Phase III studies where the patient populations are relatively large and homogeneous and consistently have measurable disease. Within our Phase I evaluation, we have identified the dose-limiting toxicity of 4-DMDR and described in broad terms its pharmacokinetic behavior. We observed no tumor regression in this study, but the number of patients with measurable disease in any diagnostic category was small; moreover, this study did not include any patients with leukemia, the disease in which daunorubicin has major clinical utility.

When administered i.v., 4-DMDR produced dose-related mye-
The plasma concentration time curves for i.v. 4-DMDR are presented. The chart shows the concentration of 4-DMDR and 4-DMDR-ol after a 50-mg/sq m dose of 4-DMDR (single p.o. administration).

The nonhematological toxicity observed in our study is less marked than that reported for daunorubicin or doxorubicin. Tan et al. (20) reported a 60% incidence of gastrointestinal complaints and a 15% incidence of stomatitis with daunorubicin; doxorubicin produced a 50% incidence of gastrointestinal complaints, a 71% incidence of stomatitis, and an 80% incidence of alopecia (19). Blum and Carter (4) reported similar results when reviewing the toxicity of doxorubicin reported by 5 major cooperative groups.

In patients given the p.o. preparation, myelosuppression was noted in 12 of 26 evaluable trials of 40 mg/sq m. Myelosuppression at a dose of 50 mg/sq m was seen in 10 of 12 trials. However, given the wide range of nadir values, it can be concluded that absorption may be erratic. The p.o. route of administration produced more nausea and vomiting (16 episodes of 62 treatment courses; 26%) than that seen with the i.v. route; dividing the dose over 3 days did not alter its incidence. Alopecia was seen in 33% of patients and diarrhea, in 10%.

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The plasma concentration time curves for i.v. 4-DMDR are triphasic, similar to those seen for doxorubicin (21). Furthermore, the $t_{1/2}$ and overall shape of the 4-DMDR curves are remarkably similar to those seen for doxorubicin (3, 21). There is, however, a striking difference in the accumulation and prolonged retention of 4-DMDR-ol seen following both i.v. and p.o. administration. Elevated levels of 4-DMDR-ol in the range of 10 to 20 ng/ml persisted 48 hr after the administration of 4-DMDR at doses of 12.5 mg/sq m i.v. and 50 mg/sq m p.o. in all patients studied. Moro et al. (17) have described similar pharmacokinetic patterns for 4-DMDR and 4-DMDR-ol. Comparable persistence of one reduced metabolite has been reported for daunorubicin (15) and Carminomycin (9, 18) but not for doxorubicin or 4'-epidoxorubicin. Casazza et al. (6) tested this metabolite in the P388 murine leukemia model and found 4-DMDR-ol more potent than daunorubicin and as potent as 4-DMDR; this may contribute to the greater potency of the drug in vivo. Comparison of the areas under the curves following i.v. and p.o. administration in our study suggests a bioavailability for 4-DMDR of approximately 32 to 35%.

In disease-oriented efficacy assessment in patients with solid tumors, including lymphoma, we suggest 12.5 mg/sq m every 21 days as the starting dose of the i.v. preparation for Phase II trials. In the absence of significant myelotoxicity, subsequent doses should be escalated by 2.5 mg/sq m. The suggested p.o. dose for good risk patients is 40 mg/sq m at 21-day intervals with escalation by 10 mg/sq m or deescalation by 5 mg/sq m as required by the observed toxic effects. These doses are in general agreement with earlier Phase I studies of both the i.v. and p.o. preparation (5, 16).

This Center has already begun Phase II trials of 4-DMDR in acute leukemia using the i.v. preparation. Daghestani et al. (10) have begun with multiples of the solid tumor dosage, i.e., 10 mg/sq m/day, twice; 10 mg/sq m/day, 3 times; 12.5 mg/sq m/day, 3 times, etc. Their preliminary observations demonstrate that 4-DMDR can induce complete remission in acute lymphoblastic and nonlymphoblastic leukemia (10). Phase II trials of 4-DMDR are also underway in a variety of solid tumors.

REFERENCES


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