Phase I Study of Doxil-Cisplatin Combination Chemotherapy in Patients with Advanced Malignancies

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ABSTRACT

Purpose: Our first objective was to evaluate the feasibility of administering a combination of Doxil, a pegylated liposome formulation of doxorubicin, and cisplatin and to determine the maximum tolerated dose of the combination. A secondary objective was to examine Doxil peak and 7-day postinjection plasma levels at the various dose levels tested.

Methods: Patients with advanced solid tumors were treated every 4 weeks with cisplatin on day 1 and Doxil on day 2. In the first three dose levels, the dose of Doxil was fixed at 40 mg/m²; whereas the dose of cisplatin was escalated from 40 to 50 and 60 mg/m². At the fourth and fifth dose levels, the dose of cisplatin was fixed at 60 mg/m², whereas the dose of Doxil was escalated to 50 and to 60 mg/m². Plasma Doxil (doxorubicin-equivalent) levels were measured by a high-performance liquid chromatography assay with fluorescence detection at 1 h and 7 days after infusion of Doxil.

Results: Twenty-six patients entered the study. Twenty-four patients completed a minimum of 2 courses and were fully assessable for toxicity and efficacy. Eighteen patients had received prior chemotherapy, 11 of them with anthracycline-containing regimens. A total of 177 courses were administered within the study. In 12 patients, cisplatin was discontinued after 1 to 13 courses, and Doxil was continued alone for 1–22 courses. All other patients received both drugs until discontinuation of therapy. The dose-limiting toxicities were neutropenia and mucositis. Grade 4 neutropenia was seen in 3 patients (one with neutropenic fever) at doses levels 4 and 5. Grade 3 mucositis was observed in 4 patients at dose levels 3, 4, and 5. In contrast, the most severe palmar-plantar erythrodysesthesia manifestation was grade 2 seen in 1 patient only. Tumor responses included seven partial responses, of which three were in ovarian cancer patients. In four of seven responders, the time to disease progression exceeded 1 year. Doxil 1-h (Cmax equivalent) levels were assessed in 20 patients. The mean Doxil Cmax (mg/l plasma) increased gradually with dose escalation from 14.7 ± 1.9 for 40 mg/m², to 17.3 ± 3.0 for 50 mg/m², and 23.3 ± 5.5 for 60 mg/m². The 60 mg/m² Cmax was similar to data obtained in parallel clinical studies at our institution with single-agent Doxil at 60 mg/m². However, the 7-day Doxil postinfusion levels were significantly lower in patients receiving the Doxil-cisplatin combination than in those receiving single-agent Doxil.

Conclusion: Doxil can be administered at full maximum tolerated dose (50 mg/m² every 4 weeks) in combination with 60 mg/m² cisplatin, with no evidence of major overlapping toxicities. Palmar-plantar erythrodysesthesia incidence and severity appears to be diminished, in comparison with data available for single-agent Doxil. Plasma concentration data point to an accelerated clearance of Doxil when administered after cisplatin.

INTRODUCTION

The anthracycline antibiotic doxorubicin is one of the most widely used antineoplastic agents and the mainstay of chemotherapy for lymphomas and a variety of solid tumors. Unfortunately, toxicity limits the therapeutic activity of doxorubicin and may preclude adequate dosing. Development of doxorubicin encapsulation in liposomes is one of the attempts to improve the therapeutic index of the drug.

Pegylated liposomal doxorubicin (Doxil, also known as Caelyx) is a novel formulation of doxorubicin in long-circulating (Stealth) liposomes that drastically changes the drug pharmacokinetics and biodistribution (1). The formulation markedly lengthens liposome circulation time by retarding reticulo-endothelial system clearance. Eventually, large numbers of liposomes are extravasated through the abnormally permeable vessels characteristic of many tumors, resulting in enhanced liposome deposition in tumors (2, 3). The toxicity profile of Doxil is characterized by dose-limiting mucocutaneous toxicities, mild myelosuppression, minimal alopecia, and no apparent cardiac toxicity (4). Doxil appears to be the most active agent available for Kaposi’s sarcoma (5, 6) and has shown significant activity against a variety of solid tumors (reviewed in Ref. 7), specifically in recurrent epithelial ovarian carcinoma (8, 9) and metastatic breast cancer (10, 11).

Cisplatin is one of the most potent chemotherapeutic agents available and forms the basis of many standard combination chemotherapy regimens. Cisplatin is used in combination with doxorubicin in the treatment of a variety of solid tumors. These two agents have different mechanisms of action, show no cross-resistance, and their toxicities do not overlap. Because Doxil appears to be a promising form of delivering doxorubicin with decrease of some of the most problematic toxicities (cardiac...
toxicity and myelosuppression), a combination with cisplatin is likely to be tolerated without enhanced toxicity, which may enable us to deliver to patients optimal doses of both agents and achieve significant advantages over standard cisplatin-doxorubicin combination.

The principal objectives of the present study were to evaluate the feasibility of administering a combination of Doxil and cisplatin and to determine the MTD of the combination. In addition, Doxil plasma levels were assessed in subgroup of patients and compared with our records for patients receiving Doxil as single agent (11, 12).

PATIENTS AND METHODS

Study Design. The study reported herein was a single-institution Phase I trial at the Hadassah Medical Center. Between February 1997 and October 1998, 26 patients were enrolled.

The starting dose of Doxil was 40 mg/m² combined with 40 mg/m² cisplatin every 4 weeks. Doses of Doxil and cisplatin were escalated according to a planned sequence (Table 1), covering a range of 40–60 mg/m² for both drugs. A minimum of 4 patients receiving at least 2 courses of treatment were enrolled per dose level. At each dose level, the study progressed to the next level if no patient experienced nonhematological toxicity of grade 3 or hematological toxicity of grade 4 during the two first dosing cycles. If only one patient experienced grade 3 or 4 toxicity, up to 4 subsequent patients were to be accrued at the same dose level until the dose tolerance could be accurately assessed. If two or more patients experienced grade 3 or 4 toxicity per dose level, then this level was declared as the initial toxic dose and the preceding level was considered as the MTD.

Eligibility Criteria and Follow-Up. Patients with histologically documented advanced solid malignancies refractory to conventional therapy or for whom no effective therapy exists were candidates for this study. Eligibility criteria included: age ≥18 years; Karnofsky performance status score ≥60%; no prior chemotherapy or radiotherapy within 4 weeks of entering the study; WBC count ≥3,500/mm³, neutrophil count ≥1,500/mm³, platelet count ≥75,000/mm³, and hemoglobin ≥10 g% (with or without transfusion); total bilirubin ≤25 µl; creatinine ≤200 µl; and left ventricle ejection fraction ≥50% by radionuclide ventriculography (MUGA scan) or echocardiography. Prior treatment with anthracyclines was allowed only if the cumulative dose of doxorubicin was <400 mg/m². The study was approved by the Hadassah institutional review board, and patients were required to provide signed, witnessed informed consent.

Pretreatment evaluation included a complete history and physical examination and documentation of performance status. Laboratory evaluation included a complete blood count, chemistry panel with liver and renal function tests, prothrombin time, and serum tumor marker levels if relevant to tumor condition. All patients had a pretreatment 12-lead electrocardiogram and cardiac ejection fraction evaluation. Radiographic evaluation included a chest radiograph and any other imaging examinations (computed tomography scan and ultrasonography) indicated by the type and site of the malignancy. Before each new treatment cycle, vital signs, weight, symptom-oriented physical check, Karnofsky status assessment, complete blood count, chemistry panel with liver and renal function tests, and report on adverse events occurring after the previous dose were obtained. During the first cycle, a complete blood count was repeated on a weekly basis. From the second cycle and onward, a complete blood count was performed before treatment and 2 weeks after each dose. After a 300 mg/m² cumulative dose of Doxil, cardiac ejection fraction was reevaluated by MUGA scan or echocardiography.

Treatment was administered until disease progression or dose-limiting toxicity. All patients who received one or more courses of cisplatin and Doxil were evaluable for toxicity. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria. For the sake of clarity, PPE grades 3–4 always entailed a situation in which simple physical activities (writing, clenching fists, and walking with closed shoes) were highly painful or unfeasible.

For stomatitis and PPE, dose-limiting toxicity was defined as any grade 3 or 4. For patients with grade 3 or 4 toxicity, the dose of subsequent courses was reduced by 25%. Patients were retreated only after the toxicity grade returned to 0 to 1. If necessary, the dosing intervals could be increased by 1 or 2 weeks to enable resolution of toxicity.

For myelosuppression, dose-limiting toxicity was defined as grade 4. In case of grade 3 neutropenia or thrombocytopenia, the study regimen was withheld until toxicity resolved to grade 0–1 (neutrophil count ≥1,500; platelets ≥75,000), after which study treatment was resumed with no dose modification. If grade 4 neutropenia (neutrophil count <500) or thrombocytopenia (platelet count <25,000) developed, therapy was withheld until resolved to grade 0–1 and resumed at a 25% dose reduction. Granulocyte-colony stimulating factor or granulocyte/macrophage-colony stimulating factor were allowed under specific circumstances in this study, in patients who showed prolonged neutropenia or in the occurrence of febrile neutropenia in a prior cycle of treatment.

Antitumor responses were evaluated after the first 2 courses and thereafter every 3 courses by physical examination, imaging radiograms, and, when indicated, tumor markers. Patients receiving ≥2 courses were considered assessable for antitumor response. The criteria for evaluating responses were defined as reported previously (4) and included the following.

### Table 1: Dose levels

<table>
<thead>
<tr>
<th>Dose level</th>
<th>No. of patients</th>
<th>Cisplatin, mg/m², day 1</th>
<th>Doxil, mg/m², day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>60</td>
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<tr>
<td>4</td>
<td>5</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

*Cycle every 4 weeks.

The abbreviations used are: MTD, maximum tolerated dose; MUGA, multigated radionuclide ventriculography; PPE, palmar-plantar erythrodysesthesia.
categories: complete response, partial response, stable (including improvement), and progressive disease. Time to disease progression and survival were defined as number of months from start of therapy until documentation of disease progression or death, respectively.

**Administration of Treatment.** All patients were hospitalized for 24 h for treatment. Doxil was obtained from ALZA Corp. (Mountain View, CA) and cisplatin from Teva Pharmaceuticals (Petach Tikva, Israel). Patients were hydrated with physiological saline and hypertonic mannitol or, when indicated, furosemide. Immediately prior to cisplatin infusion, antiemetic premedication including dexamethasone (8–20 mg) and ondansetron (8–16 mg) or granisetron (3 mg) was administered. Cisplatin was given in 150 ml of 0.9% sodium chloride solution, followed by adequate infusion of saline. The next morning, 12–18 h after cisplatin infusion, patients received Doxil diluted in 250 ml of 5% dextrose (Baxter, Deerfield, IL) without further antiemetic therapy. Doxil infusion was given over 1–2 h, beginning with a slow drip rate of 0.1–0.2 mg/min and reaching an average rate of 1 mg/min.

**Analysis of Plasma Doxil Levels.** Blood samples (4 ml) were collected into EDTA-containing tubes 1 h after completion of Doxil infusion and 7 days later. Blood was immediately stored at 5°C. Plasma was separated by centrifugation within 24 h and stored at −20°C. Extraction of doxorubicin from plasma and determination by an isotropic high-performance liquid chromatography system with fluorescence detection was as described in detail previously (13). On the basis of prior experience (11), the 1-h postinfusion sample was considered roughly indicative of the peak plasma level or $C_{\text{max}}$ of Doxil.

**RESULTS**

**Patient Characteristics.** Twenty-six patients, whose characteristics are listed in Table 2, entered this study. There were 10 female and 16 male patients with a median age of 56 years (range, 21–73 years) and a median performance status of 80% (range, 60–90%). There were 10 different types of tumors, the most frequent being soft tissue sarcoma, non-small cell lung cancer, ovary, mesothelioma, and prostate. The majority of the patients (18 of 26) had been exposed to chemotherapy before entering the study, with 11 of them having been treated with anthracycline-containing regimens. The total number of courses was 177. The median number of courses per patient was 5 (range, 1–22). In 12 patients, cisplatin was discontinued after 1–13 courses, and Doxil was continued alone for 1–22 courses. One patient received only 1 course of therapy, discontinued the treatment because of social problems, and was not assessable for skin toxicity (which, in most instances, requires at least two cycles of Doxil to manifest) nor for antitumor response. Another patient received 70 mg of free doxorubicin in addition to his scheduled therapy because of an error of the nursing team. Because of this protocol violation, he was not available for evaluation of toxicity and antitumor response. Thus, 24 fully evaluable patients remained.

**Treatment-related Toxicities.** Neutropenia was the most prominent and dose-limiting hematological side effect at the dose levels tested. On the basis of data from the first two cycles, grade 3 to 4 neutropenia was observed in 7 patients, with 1 case at dose level 2 and 2 cases at each of dose levels 3, 4, and 5. It was complicated by neutropenic fever in only 1 instance. Median nadir counts of granulocytes for all dose levels tested were in the range of 2,600–4,500/μl for the first cycle and 1,100 to 4,000/μl for the second cycle, suggesting a slight trend to lower nadirs after the second cycle (Table 3). However, the range was broad, and in some patients, no significant neutropenia was detected. Also, in most instances of granulocytopenia, there was quick recovery of the cell counts within 3–7 days. Nadir counts were observed either on day 14 or day 21 after chemotherapy.

Thrombocytopenia was mild, reaching grade 3 in only 2% of the cycles (Table 3). No grade 4 thrombocytopenia was observed. Treatment-related anemia was also mild. Grade 3 anemia was documented in 3.5% of the cycles. In one patient, grade 4 anemia that required blood transfusion was reported, and it was attributable to massive tumor-related bleeding. Median nadir values of hemoglobin were >8.7 g% at all dose levels.

Of note, one patient with recurrent ovarian carcinoma, while on partial remission of her underlying disease, died of acute myelogenous leukemia that developed 25 months after the start of treatment. This patient had received carboplatin, cyclophosphamide, and paclitaxel in the past. The respective contribution of the various drugs received by the patient to the development of acute leukemia is not known.

The major nonhematological adverse effect was mucositis in the form of stomatitis-pharyngitis (Table 4). Mucositis was the second dose-limiting toxicity of this combination regimen, reaching grade 3 in 4 of 17 patients treated at the highest three dose levels. Also (not shown in Table 4), one patient at dose level 5 developed grade 4 mucositis after the fourth cycle. In contrast, only 1 case of grade 1 mucositis was observed at the 2 lowest dose levels. Thus, severity and incidence of mucositis increased clearly at higher dose levels (Table 4).

Regarding PPE, no grade 3 or 4 was reported in the first three courses at any dose levels. Grade 2 PPE was recorded in only 1 of 8 patients at dose level 5. Grade 1 PPE was seen in 3
patients, at dose levels 2, 4, and 5 (1 each). After ≥4 courses of therapy, we observed two more events of PPE, grade 2 and grade 3, at dose levels 1 and 5, respectively. Thus, PPE was not an important side effect for this cisplatin-Doxil combination, at least on a short-term (3 cycles) treatment basis.

Other nonhematological toxicities observed included the following: mild to moderate alopecia in 2 patients; skin pigmentation spots, which were usually reversible, in 2 patients; protracted nausea in 1 patient; and grade 2–3 fatigue in 3 patients with a large bulk of tumor during the first cycle of therapy, a symptom that did not reappear in subsequent cycles. In addition, there were 4 patients who experienced cisplatin-related toxicities, in whom cisplatin was discontinued: grade 1 nephrotoxicity (shown by a rise in creatinine to 150 μM) in 1 patient at dose level 4 after one course; ototoxicity (hearing loss) in 2 patients at dose levels 2 and 5, after 4 and 5 courses of cisplatin; and peripheral neurosensory toxicity in 1 heavily cisplatin-pretreated patient after 13 courses. Because of difficulties in compliance with repeated treatment, there were another eight patients in whom cisplatin was discontinued after five or more cycles, and Doxil was continued alone as maintenance therapy, thus avoiding the need for hydration and hospitalization.

Monitoring of cardiac function was performed by MUGA scan or echocardiography at baseline and serially in patients receiving cumulative doses >300 mg/m². A total of 8 patients received a cumulative dose of Doxil ≥450 mg/m² (including a patient who reached a cumulative dose of 1160 mg/m²), and remained with normal cardiac ejection fractions. Clinical congestive heart failure did not occur.

**Dose-limiting Toxicities and MTD.** The dose-limiting toxicities observed were: 1 patient with grade 3 mucositis at dose level 3; 1 patient with grade 3 mucositis and grade 4 neutropenia at dose level 4; and 3 patients with grade 3 mucositis (2 patients) and grade 4 neutropenia (2 patients, 1 of them with neutropenic fever) at dose level 5. On the basis of the protocol requirement of two events of dose-limiting toxicity per dose level in different patients during the first two cycles, dose level 5 was considered unacceptably toxic, and the MTD was established at dose level 4, i.e., 50 mg/m² Doxil in combination with 60 mg/m² cisplatin every 4 weeks. As to cisplatin dose, it is still possible that it can be escalated slightly further, especially with the help of hematopoietic colony-stimulating factors. However, because this study was designed to examine toxicity within a maximal target dose of 60 mg/m², we did not proceed with further escalation.

**Antitumor Activity.** The antitumor responses obtained in 24 assessable patients receiving at least 2 cycles of treatment are listed in Table 5. Seven patients achieved a partial response. In all but 1 patient, these responses were based on disease measurable by computed tomography scan. In 1 patient with prostate cancer, the response was based on a >50% decrease of the prostate-specific antigen level from baseline on at least two consecutive measurements 1 month apart.

**Table 3** Myelosuppression

<table>
<thead>
<tr>
<th>Dose level</th>
<th>First course</th>
<th>Second course</th>
<th>First course</th>
<th>Second course</th>
<th>First course</th>
<th>Second course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Granulocytes (× 10^3/μl)</td>
<td>Platelets (× 10^3/μl)</td>
<td>Hemoglobin (g/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4.5 (3.7–6.8)</td>
<td>3.8 (3.2–4.6)</td>
<td>367 (228–504)</td>
<td>290 (212–346)</td>
<td>11.6 (8.8–12.8)</td>
<td>11.9 (11.7–12.4)</td>
</tr>
<tr>
<td>2</td>
<td>2.6 (0.9–8.7)</td>
<td>2.2 (1.2–6.0)</td>
<td>137 (105–335)</td>
<td>208 (86–319)</td>
<td>11.7 (10.5–13.8)</td>
<td>11.6 (8.8–13.0)</td>
</tr>
<tr>
<td>3</td>
<td>2.6 (1.4–3.7)</td>
<td>1.1 (0.7–4.7)</td>
<td>95 (70–146)</td>
<td>107 (42–183)</td>
<td>8.8 (5.0–11.6)</td>
<td>9.5 (8.2–10.9)</td>
</tr>
<tr>
<td>4</td>
<td>3.2 (0.2–4.4)</td>
<td>1.7 (1.5–2.4)</td>
<td>286 (30–476)</td>
<td>265 (155–413)</td>
<td>9.0 (7.5–11.7)</td>
<td>8.7 (8.6–11.0)</td>
</tr>
<tr>
<td>5</td>
<td>4.4 (0.3–5.6)</td>
<td>4.0 (0.4–4.2)</td>
<td>231 (70–448)</td>
<td>154 (34–505)</td>
<td>11.0 (8.7–12.7)</td>
<td>11.1 (8.9–11.9)</td>
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</table>

* The patient numbers for each dose level are as shown in Table 1.

**Table 4** Mucositis

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Grade 1</th>
<th>Grade 2</th>
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<th>Grade 4</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1/4</td>
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<td>0/4</td>
<td>0/4</td>
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<tr>
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<td>5</td>
<td>1/8</td>
<td>0/8</td>
<td>2/8</td>
<td>0/8</td>
</tr>
</tbody>
</table>

* Based on the first 2 cycles, except for 1 patient who received only 1 course at dose level 1 and discontinued therapy thereafter.

**Table 5** Antitumor response

<table>
<thead>
<tr>
<th>Response and no. of patients</th>
<th>Time to progression (mo)</th>
<th>Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response (n = 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer (n = 3)</td>
<td>11, 23, 32</td>
<td>16, 25, 37+</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Hepatoma</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Neuroendocrine cancer</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Stable (n = 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>12</td>
<td>28</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>8</td>
<td>13</td>
</tr>
</tbody>
</table>

* Response based on >50% drop of the prostate-specific antigen level from baseline on at least two consecutive measurements 1 month apart.
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2.1 mg/l; groups receiving 60 mg/m² were well matched in terms of sex distribution (male:female ratio, 5:3 for Doxil-cisplatin and 7:6 for Doxil only) and median age [57 years (range, 21–73 years) for Doxil-cisplatin and 60 years (range, 32–75 years) for Doxil only]. Bars, SD.

Fig. 1 Cₘₐₓ (plasma concentration at 1-h postinfusion) of Doxil in patients receiving Doxil-cisplatin (Doxil dose, 40, 50, or 60 mg/m²) or Doxil only (Doxil dose, 60 mg/m²; from Refs. 11, 12). Both of the groups receiving 60 mg/m² were well matched in terms of sex distribution (male:female ratio, 5:3 for Doxil-cisplatin and 7:6 for Doxil only) and median age [57 years (range, 21–73 years) for Doxil-cisplatin and 60 years (range, 32–75 years) for Doxil only]. Bars, SD.

Fig. 2 Fraction of Cₘₐₓ remaining in plasma at 7 days postinfusion of Doxil in patients receiving Doxil-cisplatin (Doxil dose, 60 mg/m²) or Doxil only (Doxil dose, 60 mg/m²; from Refs. 11, 12). The difference between the two groups was statistically significant (P = 0.0173, t test). Both groups were well-matched in terms of sex distribution (male:female ratio, 5:3 for Doxil-cisplatin and 7:6 for Doxil only) and median age [57 years (range, 21–73 years) for Doxil-cisplatin and 60 years (range, 32–75 years) for Doxil only]. Bars, SD.

from 14.7 ± 1.9 for 40 mg/m², to 17.3 ± 3.0 for 50 mg/m², and 23.3 ± 5.5 for 60 mg/m² (mean ± SD, in mg/l). As seen in Fig. 1, the drug levels at 60 mg/m² were similar to those obtained in a group of patients with breast and prostate cancer receiving single-agent Doxil also at 60 mg/m² (23.9 ± 4.7 mg/l) within the frame of parallel clinical studies (11, 12), indicating that the peak plasma levels (Cₘₐₓ) of Doxil are not affected by cisplatin preinfusion. However, when the 7-day postinfusion levels were examined at the 60 mg/m² dose level, patients receiving Doxil after cisplatin had significantly lower doxorubicin levels (3.3 ± 1.0 mg/l; n = 8) than those receiving single-agent Doxil (5.3 ± 2.1 mg/l; n = 13) with P = 0.0195 (t test). This observation remains valid when the 7-day postinfusion Doxil levels are expressed as a percentage of the 1-h postinfusion levels (Fig. 2) and suggests that the first week of clearance of Doxil is accelerated in patients receiving a cisplatin preinfusion. It should be noted that none of the control group (breast and prostate cancer) patients had received treatment with cisplatin or carboplatin, although all breast cancer patients had been pretreated with other forms of chemotherapy prior to entering the Doxil study.

DISCUSSION

The anthracycline antibiotic doxorubicin and cisplatin are potent anticancer compounds widely used in a broad spectrum of malignancies. Because of their different and nonoverlapping toxic effects, there has been considerable interest in combining them. Cisplatin and doxorubicin are widely used as the main components of many chemotherapy regimes in the treatment of a variety of advanced cancers.

However, cumulative dose-dependent myocardial damage and high degree of myelosuppression associated with doxorubicin may result in life-threatening toxicity and entail often a significant dose compromise and even treatment interruption in responding patients. This is not the case with regard to Doxil, which has a markedly different toxicity profile. Recently reported data in a group of 40 patients receiving between 500 and 1500 mg/m² (median, 635 mg/m²) suggest that Doxil can be administered at high cumulative doses with none of the patients developing clinical congestive heart failure or ventriculographic signs of drug-induced damage (14). This observation is concordant with results of animal studies pointing to reduced cardiotoxicity of Doxil as compared with free doxorubicin (15) and with clinical data reporting low endomyocardial biopsy scores in 10 Doxil-treated patients with AIDS-related Kaposi’s sarcoma relative to controls receiving free doxorubicin (16). In addition, Doxil causes mild myelosuppression (7), in contrast to profound neutropenia associated with bolus administration of doxorubicin at the standard 3-week schedule without growth factor support. Unfortunately, the MTD of Doxil (50 mg/m² every 4 weeks) is actually lower than that of conventionally administered doxorubicin (60 mg/m² every 3 weeks) because of dose-limiting mucocutaneous toxicities, resulting from the accumulation of large amounts of Stealth liposomes in skin and probably also mucosas (7).

Besides toxicity considerations, a unique feature of Doxil is its high tumor accumulation (17–19), attributable to the ability of Stealth liposomes to extravasate across the leaky microvasculature of tumors (20). This feature can make certain tumors more susceptible to the antitumor effects of Doxil relative to free doxorubicin. In the specific case of epithelial ovarian cancer, Doxil is a recognized option in the treatment of recurrences (8, 9), whereas the role of doxorubicin is controversial (21).

Because Doxil appears to be a promising form of delivering doxorubicin with potential enhancement of antitumor activity and a decrease of some of the undesirable toxicities, this drug is a candidate to replace doxorubicin in cisplatin-doxorubicin regimes and perhaps other combination chemotherapy regimes. The rationale for a cisplatin-Doxil combination is also based on the fact that cisplatin and Doxil toxicities do not overlap: on the one hand, the nephrotoxicity, neurotoxicity, and ototoxicity of cisplatin are totally absent from Doxil; on the other hand, the mucositis and skin toxicity of Doxil are totally absent from cisplatin. Therefore, the Doxil-cisplatin combination is likely to
be tolerated without enhanced toxicity. The choice of cisplatin over carboplatin was based mainly on the fact that carboplatin is more myelosuppressive than cisplatin, and, therefore, the risk of overlapping myelosuppression with Doxil is greater.

All of this led us to undertake a Phase I trial with Doxil and cisplatin combination chemotherapy. We chose the 4-week schedule for the combination because of prior observations indicating that dose, schedule, and intensity of Doxil are important determinants of PPE. Thus, doses of 60, 50, and even 45 mg/m² of single-agent Doxil are intolerable with regard to skin toxicity on a 3-week schedule and have to be delivered on a 4-week or longer schedule (4, 8, 10). The dose-limiting toxicities in this study were a combination of mucositis and neutropenia. Mucositis was more frequent and severe in patients receiving higher dose levels. It reached grade 3 in 4 of 17 patients treated at dose levels 3, 4, and 5. The incidence and severity of mucositis reported in this study are roughly similar to those in patients receiving single-agent Doxil at similar doses (4, 8, 10, 11, 13). This is consistent with the finding that Doxil C_{max} values are not affected by cisplatin (Fig. 1) and with the reported observation of a direct correlation among dose, C_{max} and mucositis (11).

Surprisingly, neutropenia was found to be a major dose-limiting side-effect of the Doxil-cisplatin combination. Thus, 3 cases of grade 4 neutropenia (1 with neutropenic fever) were detected among 13 patients treated at dose levels 4 and 5. It is noteworthy that recovery from severe neutropenia was relatively quick and, in all cases, within 7 days. Yet, the fact that neutropenia was one of the dose-limiting toxicities was quite unexpected. On the one hand, neutropenia is not a prominent feature of cisplatin as a single agent. On the other hand, Doxil as a single agent is generally associated with mild neutropenia. For instance, Gordon et al. (9) reported grade 4 neutropenia in 4% of 89 patients receiving Doxil 50 mg/m² with only 1 case of neutropenic fever. Therefore, attention should be paid to the possibility of a synergistic myelosuppressive effect when cisplatin and Doxil are combined.

An important and encouraging observation of the present study was the low incidence and severity of PPE in relation to data available for single-agent Doxil (4, 8, 10, 11, 12). A similar finding has been reported in abstract form using a slightly different regime of cisplatin and Doxil (22). The most severe PPE manifestation reported in our study during the first 3 cycles was grade 2, which occurred in only 1 patient at dose level 5. For comparison, grades 2 and 3 PPE have been reported in 34% of 32 breast cancer patients treated with single-agent Doxil at 45 mg/m² every 4 weeks (10) and in 31% of 89 ovarian cancer patients treated with treated with single-agent Doxil at 50 mg/m² every 4 weeks (9). Our limited pharmacokinetic data may explain these results. A positive correlation between risk of PPE and plasma half-life of Doxil has been found previously (11). Patients receiving 60 mg/m² of Doxil after cisplatin had significantly lower 7-day postinfusion levels than those receiving single-agent Doxil (Fig. 2). This change cannot be attributed to the corticosteroid premedication, because no pharmacokinetic changes were observed when we used a similar premedication regime in a recent study combining amifostine and Doxil (23). An accelerated clearance of Doxil in patients receiving the cisplatin-Doxil combination, as suggested by the 7-day plasma level data, may explain the low incidence and severity of PPE observed in this study. Cisplatin has been shown to cause in vitro and in vivo murine macrophage activation (24–26). If these results are extrapolated to human macrophages, one possible explanation is that accelerated clearance of liposomes after cisplatin treatment is related to transient macrophage activation induced by cisplatin.

Antitumor responses to the combination of Doxil and cisplatin were observed in a variety of tumor types, some of them with remarkably long times to disease progression exceeding 1 year in several cases. Of note, 3 of 4 ovarian cancer patients responded with objective partial response. In contrast, none of 6 patients with soft tissue sarcoma responded. Both groups of patients had been pretreated with chemotherapy. Lack of response of sarcomas to Doxil has been reported (27).

The results of our study established the MTD at 50 mg/m² of Doxil in combination with 60 mg/m² of cisplatin every 4 weeks. This indicates that Doxil can be given at full MTD and recommended dose intensity (12.5 mg/m²/week) when combined with cisplatin. Thus far, in other combinations of Doxil with different anticancer drugs (taxanes, vinorelbine, and gemcitabine), there has been a need to trim Doxil dose intensity to ≤10 mg/m²/week (28–33). In conclusion, the present study has identified the Doxil-cisplatin combination as a promising regimen for further evaluation in the treatment of malignant tumors, exhibiting a different toxicity profile from single-agent Doxil.

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Phase I Study of Doxil-Cisplatin Combination Chemotherapy in Patients with Advanced Malignancies

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