A phase I and pharmacokinetic study of docetaxel combined with Doxil (pegylated liposomal doxorubicin) without and with granulocyte colony stimulating factor

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The purpose of this study was (i) to determine the maximum tolerated dose (MTD) of docetaxel that can be administered in combination with Doxil, given without and with granulocyte colony stimulating factor (G-CSF), (ii) to define the pharmacokinetics (PK) of docetaxel when used in combination with Doxil, and (iii) to make preliminary observations on the anti-tumor activity of this combination in patients with metastatic solid tumors. Thirty-seven patients with metastatic cancer were enrolled. Courses were repeated every 3 weeks. Patients received a fixed dose of Doxil 30 mg/m^2 in combination with escalating doses of docetaxel ranging from 40 to 100 mg/m^2. After encountering dose-limiting febrile neutropenia, subsequent escalation was accomplished with G-CSF support. Selected patients at the recommended phase II dose underwent PK evaluation. The most common toxicity observed was neutropenia. Dose-limiting toxicity (30 mg/m^2 Doxil + 80 mg/m^2 docetaxel) was febrile neutropenia in three of six patients treated without G-CSF. Major non-hematological toxicities included alopecia, mucositis and hand–foot syndrome, and were observed after cumulative doses of chemotherapy. Objective responses (complete/partial) were documented in eight of 37 patients (four with breast cancer) and stable disease was seen in 17 patients. PK studies showed an increased tissue retention (decreased clearance) of docetaxel when given with Doxil. The recommended phase II dose of Doxil/docetaxel is 30/60 mg/m^2, q3 weeks, without G-CSF. Further dose escalation to 30/80 mg/m^2 is safe with G-CSF support. Anti-tumor activity, particularly against breast cancer, was observed at various dose levels. Our observations should provide evidence for phase II studies of this combination in patients with breast cancer and other anthracycline/taxane-sensitive cancers. *Anti-Cancer Drugs* 15:119–125 © 2004 Lippincott Williams & Wilkins.

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Introduction

Doxil (pegylated liposomal doxorubicin) confers considerably less myelosuppression than its parent compound, doxorubicin, at doses that have demonstrated clinical activity. Doxil as a single agent has demonstrated activity in Kaposi's sarcoma [1] and platinum-resistant ovarian cancer [2,3]. In breast cancer, phase II trials of single-agent Doxil have suggested activity comparable to that of doxorubicin, with response rates of 31% in a first-line metastatic trial [4]. In addition to reduced myelosuppression, repeated administrations do not appear to lead to clinical cardiac toxicity [5]. Thus, there is an interest in establishing the role for such formulations alone or as part of standard regimens in a number of doxorubicin-sensitive tumors [6].

Docetaxel (Taxotere) is a semi-synthetic taxane and is one of a class of compounds that inhibit the mitotic spindle apparatus by stabilizing tubulin polymers, leading to the death of mitotic cells in the G_2/M phase of the cell cycle. Docetaxel has also been shown to phosphorylate, and thereby inactivate, the anti-apoptotic protein, BCL-2 [7]. In patients with metastatic disease, activity of this drug has been demonstrated in breast [6,8], ovarian [9] and lung cancer [10–12] as well as in hormone-refractory prostate cancer patients [13]. Docetaxel has demonstrated significant single-agent activity in anthracycline-resistant, metastatic breast cancer patients with an overall response rate of 41% [6,14].

A phase III trial by Nabholtz demonstrated a higher response rate and longer time to progression with

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doxorubicin/docetaxel (AT) compared to the commonly used regimen, doxorubicin/cyclophosphamide (AC). This outcome with AT was obtained without significant increase in cardiac dysfunction as compared to AC [15], but at a cost of greater myelosuppression. As opposed to prior experience with doxorubicin/paclitaxel combinations, no pharmacologic interaction [16] was noted for docetaxel given together with doxorubicin or epirubicin [17]. However, differences were noted with respect to the metabolism of epirubicin, both from the combination of either docetaxel or paclitaxel [17]. A more recent study by Schuller *et al.* with a limited number of breast cancer patients also reported no changes in the disposition of epirubicin, but an increase in the glucorinides of epirubin were detected [18]. These investigators also reported increases in the docetaxel AUC along with a decrease in the clearance.

A Doxil/docetaxel combination has the potential for overcoming the neutropenic and cardiac complications associated with AT. Therefore, this phase I study was initiated to explore the toxicity and document the preliminary observations on the activity of such a combination. In addition, we explored whether Doxil would have an effect on the pharmacokinetics (PK) of docetaxel. On the other hand, we did not study the effect of docetaxel on the PK of Doxil. This would require observations at very different time points than the docetaxel PK, as well as studying the patient on a cycle during Doxil alone and during combined treatment. Moreover, keeping the Doxil dose fixed at the well-tolerated dose rate of 10 mg/m^2/week, while escalating docetaxel, led to the expectation that dose-limiting toxicities (DLTs) would be attributed primarily to docetaxel effects.

Patients and methods

After approval by the Institutional Research Committee of the New York University School of Medicine, accrual was initiated in January 1998. Eligibility criteria included metastatic solid tumors with measurable or evaluable disease. Prior doxorubicin exposure (maximum 300 mg/m^2 as an adjuvant therapy) was permitted, but patients could not have received prior taxane therapy. A maximum of two prior chemotherapy regimens, either both for metastatic disease in the absence of any adjuvant chemotherapy or only one prior regimen for metastatic disease after failing adjuvant chemotherapy, was allowed. Adequate organ function defined as platelets $\geq$ 100 000/μl, granulocyte count $\geq$ 1500/μl, hemoglobin level $\geq$ 8.0 g/dl, creatinine level $\leq$ 2 mg/dl and bilirubin $\leq$ 1.5 mg/dl was required. Also, the baseline left ventricular ejection fraction by MUGA scan had to be $\geq$ 50% (lower limit of normal for the institution). All patients were expected to have an ECOG performance status of $\leq$ 2. Prior radiotherapy was allowed provided it was discontinued at least 4 weeks prior to entry and it had not been delivered to the whole pelvis or $>$ 20% of bone marrow producing areas. Protocol treatment had to await recovery from any radiation therapy toxicity. Patients were excluded if they presented with active brain metastasis, unstable angina pectoris, ventricular arrhythmias or myocardial infarction within the last 6 months of entry onto trial. All patients gave written informed consent.

Study design

This was a phase I, open-label, non-randomized, dose-finding study of Doxil/docetaxel given q3 weeks. Cohorts of at least three patients on each dose level were to be enrolled. The study was conducted at Bellevue Hospital and at the private services of the New York University Medical Center.

Doxil was provided by Alza Pharmaceuticals (Menlo Park, CA). It was administered after diluting the preparation in 5% dextrose solution (D5W). If the total dose administered was less than 80 mg, the drug was given in 250 ml of D5W. Doses of 80 mg or above were diluted in 500 ml of D5W. During the first treatment, patients were observed closely for 'flushing' reactions after being given the initial 2–3 mg (about 3 ml) as a test dose. After the first 30 min of observation free of reactions, the infusion was accelerated and completed over 1 h.

Docetaxel provided by Aventis Pharmaceuticals (Bridgewater, NJ), in 20 and 80 mg vials. It was administered immediately following Doxil through a peripheral access route after diluting the preparation in 250 ml of D5W over 1 h.

All patients were premedicated with 8 mg of dexamethasone by mouth twice daily beginning 1 day prior to chemotherapy for a total of six doses. Diphenhydramine, cimetidine or ranitidine and additional dexamethasone were administered in the event of a hypersensitivity reaction to Doxil/docetaxel. Initial cohorts of three patients were treated at each dose level. Dose modifications were defined for hematologic toxicity, hand–foot syndrome [palmar–plantar erythrodysesthesia (PPE)] and liver dysfunction. DLT was febrile neutropenia, grade 4 thrombocytopenia or any grade 3–4 non-hematologic toxicity. If a DLT occurred in one of the three initial patients at any dose level, an additional three patients were enrolled at the same dose level. Dose escalation was discontinued if DLT was observed in two or more patients at any given dose level, which defined the maximum tolerated dose (MTD). The dose immediately below the MTD was then expanded and PK studies were instituted. If febrile neutropenia was the DLT, additional accrual at the same dose level with granulocyte colony stimulating factor (G-CSF) and subsequent dose escalations, if tolerable, were planned. All treatments were performed

in the ambulatory setting. Treatment was continued until progressive disease or unacceptable toxicity.

PK measurements

The PK of docetaxel at 80 mg/m^2 and Doxil 30 mg/m^2 were studied in five patients. Blood was drawn into heparinized tubes before the start of the docetaxel infusion, and then 5, 10, 20 and 30 min, and 1, 1.5, 2, 3, 4, 5, 7 and 24 h after completion of the docetaxel infusion. The plasma was centrifuged at 1000 *g* for 10 min, aliquoted in cryovials and stored at –20°C until further analysis. The assay of docetaxel employed a validated modification of previously reported analytical methodology involving a solid-phase extraction of the drug from plasma, and reversed-phase HPLC chromatographic analytical methodology for docetaxel using a mobile phase composition of 55% 10 mM ammonium acetate, pH 4.0, and 45% acetonitrile [19,20]. The modifications involved the use of a C2-bonded reversed-phase chromatographic column (Curosil-B 3µ, 150 × 4.6 mm; Phenomenex, Torrance CA), and evaporation of the solid-phase extracted docetaxel and internal standard paclitaxel to dryness using a Speed-Vac (Forma Scientific, Farmington, NY). The validated quantitation range was 50–3500 ng/ml, with an inter-day coefficient of variation of less than 9%. Pharmacokinetic parameter estimates of the blood level decay data were obtained by a non-linear least-squares weighted regression analysis using a three-compartment continuous-infusion model available in WinNonlin version 1.5 (Pharsight, Menlo Park, CA).

Response evaluation

Physical examination and radiographic methods using computerized tomography (CT) or magnetic resonance imaging (MRI) were used to evaluate tumor size at baseline. The first CT or MRI assessment took place just prior to the third cycle of treatment and then occurred every 12 weeks thereafter. Additional studies were performed if patients' symptoms suggested progressive disease. Responses were assessed by UICC criteria [21,22].

Statistical analysis

Comparisons of toxicities between dose levels (DL) employed descriptive methods. The comparisons between the PK parameter estimates were also descriptive in nature due to the small sample size between this and previous studies.

Results

Patient population

Thirty-seven patients were enrolled and their characteristics at study entry are listed in Table 1. Breast cancer (seven patients), gynecologic malignancies (six patients) and melanoma (six patients) were the most common primary tumors. Two patients with breast cancer had a concomitant ovarian and endometrial cancer, respectively.

Table 1 Patient characteristics

Median age [years (range)]	57 (36–77)
Male/female (n=37)	17/20
Performance status (n=37)	
0	1
1	14
2	22
Primary tumor	
breast	7
gynecological (ovarian)	6 (3)
esophageal	3
head and neck	4
nasopharyngeal	1
melanoma	6
non-small cell lung	4
sarcoma (soft tissue)	2
thyroid	2
bladder	1
paraganglioma	1
No. of prior therapies	
0	11
1	20
2	6
Prior doxorubicin	4

The majority of patients were enrolled with a performance status of 2 (22 patients). Expansion of the study population was required at DL4 to evaluate the PK of docetaxel.

Chemotherapy administration

A total of 186 cycles were administered to 37 patients. Patients were given cumulative doses of docetaxel ranging from 120 to 1040 mg/m^2. Patients who received G-CSF at DL4 and 5 received a greater mean dose of docetaxel compared to those who did not.

Hematologic toxicity

Febrile neutropenia was the DLT. One of six patients at DL2 and three of six patients accrued to DL3 experienced febrile neutropenia. All patients who experienced this toxicity had received prior chemotherapy. Subsequently, the study was amended to include G-CSF (300 µg/day, day 3–7) at DL4 and 5. Of the 19 patients accrued to DL4 with G-CSF, grade 3 or 4 neutropenia was found in six patients, but only one experienced febrile neutropenia. At DL5, one of three patients experienced febrile neutropenia, so this cohort was closed. Anemia was not dose limiting, but the majority of patients (n = 32) received erythropoietin injections during the course of their treatment.

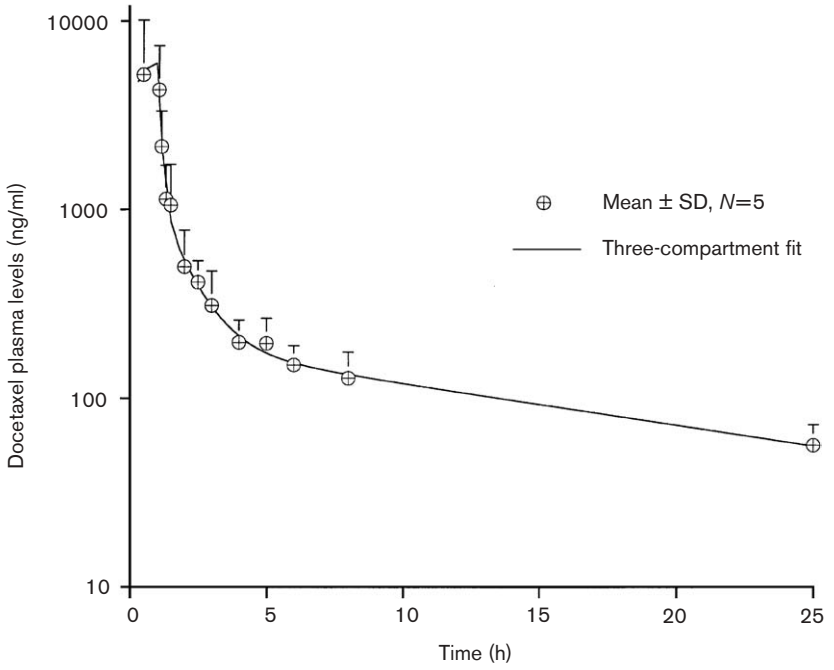
Non-hematologic toxicity

All patients experienced complete alopecia after 3 or 4 cycles of chemotherapy. The most common non-hematological toxicities were PPE and mucositis. These side-effects occurred most commonly after a median of three cycles. Only one patient (DL4) experienced grade 3 diarrhea. No cardiac events occurred. None of the patients experienced peripheral neuropathy. One patient withdrew from the study after the test dose of Doxil at

Table 2 Toxicity (grade 3–4)

Toxicity	DL1: Dox 30/Doc 40 (*N*=3)	DL2: Dox 30/Doc 60 (*N*=6)	DL3: Dox 30/Doc 80 (*N*=6)	DL4: Dox 30/Doc 80 + G-CSF (*N*=19)	DL5: Dox 30/Doc 100 + G-CSF (*N*=3)
Fatigue	0	0	0	2	0
Diarrhea	0	0	0	1	0
Mucositis	0	2	1	2	1
PPE	0	1	0	2	1
Anemia	1	3	4	4	2
Thrombocytopenia	1	0	0	3	0
Neutropenia	1	5	6	6	1
Febrile neutropenia	0	1	3	1	1

Fig. 1



Summary of mean ± SD values for docetaxel decay plots from the patients 1–5 who received docetaxel at 80 mg/m^2. The decay was fitted with a three-compartment model.

dose level 4 caused an acute hypersensitivity reaction with hypotension and shortness of breath. The reaction subsided with interruption of the infusion and i.v. corticosteroids, but the patient then refused to be re-challenged. Toxicity per dose level is outlined in Table 2.

Pharmacokinetics

Plasma levels of docetaxel were quantitated in five patients at the dose of 80 mg/m^2 and Doxil at 30 mg/m^2 (DL4 with G-CSF). A summary of the plot of mean and SD along with the triphasic fit of these data is shown in Figure 1. As summarized in Table 3, a mean initial rapid half-life of 4.4 ± 4.3 min was followed by a mean intermediate half-life of 49.6 ± 21.2 min (range 29.6–76.8 min) and a mean terminal half-life of 19.9 ± 9.1 h. A mean AUC of 8.4 ± 2.1 was determined and the mean total body clearance was 10.0 ± 2.4 l/h/m^2.

Tumor responses

Complete responses were observed in two patients, one with esophageal cancer and one with leiomyosarcoma of the uterus. Both patients with complete responses were previously untreated. Partial responses were seen in six patients: four of the seven patients with breast cancer, and one osteosarcoma and one ovarian cancer. Stable disease was seen in 17 patients (Table 4). All the patients who responded to treatment had not received prior anthracyclines [overall response rate = 22% (eight of 37) + 95%confidence interval]. Overall, eight of 37 evaluable patients (22%) had objective responses in the phase I

Table 3 Docetaxel PK parameter summary

Parameter	Patient					Average	SD
	1	2	3	4	5		
AUC (μg/ml·h)	11.5	5.9	9.0	7.9	7.5	8.4	2.1
CL (l/h/m^2)	6.9	13.5	8.9	10.2	10.7	10.0	2.4
Elimination half-life α (min)	10.8	0.1	0.8	5.2	5.2	4.4	4.3
Elimination half-life β (min)	76.8	45.5	29.6	65.7	30.2	49.6	21.2
Elimination half-life γ (h)	35.4	14.2	12.8	17.5	19.5	19.9	9.1
C_{max} (μg/ml)	4.5	1.0	3.5	4.9	4.2	3.6	1.6
Volume of distribution V_d (l)	236.1	280.7	107.2	109.0	162.6	179.1	77.3

Taxotere PK for reference: α=4 min, β=36 min, γ=11.1 h, CL=21 l/h/m^2, V_d=113 l.

Table 4 Response to treatment

DL	No. of patients				
	Complete response	Partial response	Stable disease	Progressive disease	Not evaluable
1	0	0	1 (esophageal)	2 (ovary, melanoma)	0
2	0	1[a] (breast)	2 (endometrial and lung)	3 (H & N, bladder, melanoma)	0
3	1[*] (esophageal)	2[b,*] (2 breast 1[*])	2 (vulvar and H & N)	1 (H & N)	0
4 + G-CSF	0	2[c] (1 osteosarcoma and 1 breast/endometrial)	11 (2 sarcoma, 3 breast, 1 ovary, 1 esophageal, 4 melanoma)	5 (1 lung, 2 H & N, 1 melanoma, 1 thyroid)	1 (lung)
5 + G-CSF	1[*] (leiomyosarcoma)	1[d] (ovarian)	1 (nasopharyngeal)	0	0
Total	2	6	17	11	1

[*]No prior therapy.
[a]Breast—adjuvant CMF.
[b]Two breast—one no prior tx; one adjuvant XRT/tamoxifen.
[c]One osteosarcoma—adjuvant HD-MTX; one breast/endometrial—adjuvant tamoxifen/first-line with tx/anastrazole.
[d]Ovarian—adjuvant topotecan/cisplatin.

trial. The duration of responses ranged from 9 to 39 weeks, with a median duration of 20 weeks.

Discussion

A combination of Doxil and docetaxel is deemed an attractive target for study because of promising results that had been reported with taxane and anthracycline combinations, particularly for the treatment of breast cancer [23–25]. The use of pegylated liposomal doxorubicin (Doxil) has several potential advantages over doxorubicin in such combinations. Myelosuppression is less common when the liposomal formulation is used as a single agent at the recommended doses [3] and Doxil is less likely to be associated with cardiac toxicity [26,27]. Enhanced therapeutic benefit may occur with Doxil due to greater accumulation of doxorubicin within tumor tissues [28,29]. This drug accumulation has been defined as due to 'passive targeting' and is related to the phenomenon of enhanced permeability and retention [5].

Our results demonstrate that this treatment had tolerable toxicity at doses considered adequate for both drugs and uncovered no unusual adverse events. Moreover, several objective responses were documented. In particular, four of seven patients with breast cancer achieved a partial response. The median number of cycles at each dose level studied ranged from 4.0 to 6.0, attesting to the tolerance and also the antitumor activity of this combination. The duration of responses ranged from 9 to 39 weeks, with a median duration of 20 weeks.

While respect to the combination of taxanes with anthracyclines, there has been no noted PK interactions [16,22], with the exception of effects on the metabolism of epirubicin [17,18]. However, with a small group of breast cancer patients treated in a combination study with epirubicin and docetaxel, a 34% increase in the docetaxel AUC was observed along with a decreased clearance. Therefore, for the future use of this combination of anthracyclines and taxanes, it is important to document possible PK interactions. Hence, we evaluated the PK of docetaxel when given at a dose of 80 mg/m^2 combined with Doxil 30 mg/m^2. As compared with initial phase I PK studies of docetaxel [30,31], the summary of parameter estimates from our limited study sample shows that the concomitant administration of Doxil and docetaxel resulted in an increased AUC and elimination half-life, and as a result of these two parameters, a

decreased clearance. The steady-state volume of distribution was found to be similar. However, a decreased clearance of docetaxel when given sequentially after Doxil administration cannot be attributed to the presence of free anthracycline liberated from Doxil, as plasma concentrations of free drug have been found to be negligible in other studies [28,29,32]. Unexplained effects of Doxil on docetaxel metabolism by cytochrome P450-3A4 is another possible explanation. Also, docetaxel clearance is inversely proportional to the serum concentration of α_1-acid glycoprotein [33] and effects on this component cannot be excluded. Finally, a hypothesis to explain the higher AUC of docetaxel when administered with Doxil might postulate a liposomal-facilitated tissue penetration of docetaxel in the presence of the co-administration of the Doxil. This would result in the more prolonged tissue retention observed as reflected in the around 80% longer mean γ half-life of 20 h compared with 11.1 h for from the phase I studies with docetaxel alone [30]. Such a hypothesis is consistent with the limited toxicities observed and the absence of no discernable perturbation in liver enzyme chemistries monitored in this study.

The combination of Doxil 30 mg/m^2 and docetaxel at 80 mg/m^2 with G-CSF support was a well-tolerated regimen in 11 previously untreated patients and eight previously treated patients with advanced solid tumors. While Doxil increases tissue retention and decreases docetaxel clearance, such an interaction does not alter the drug's predictability and manageable toxicities.

Our results parallel the recent findings of Sparano *et al.* [34] of a phase I study in advanced breast cancer, but also differ in important details. Their recommended phase II doses, docetaxel 75 mg/m^2 and Doxil 30 mg/m^2, were determined at a schedule of every 4 weeks, and they included a requirement for G-CSF to prevent febrile neutropenia. They subsequently explored a 3-week interval without G-CSF utilizing the doses of our DL2. In both studies, high activity in advanced breast cancer was documented. These results lend support to the subsequent exploration of this two-drug combination in several clinical trials. This combination is likely to prove suitable even in the presence of remote prior anthracycline treatment, since Doxil is unlikely to contribute to cardiac toxicity [26]. Furthermore, even in patients relapsing within 1 year of adjuvant doxorubicin, the use of Doxil might overcome partial resistance to doxorubicin in view of its greater localization and drug accumulation at tumor sites.

Another setting for this combination is metastatic breast cancer associated with Her2/*neu* overexpression. In fact, the Eastern Cooperative Oncology Group has initiated a study with the combination docetaxel plus Doxil plus trastuzumab based on the study by Sparano *et al.* [34]. In that study, the potential for cardiac toxicity is being evaluated in patients receiving up to 6 cycles of this combination. In this phase I study, no cardiac events were noted, supporting the rationale for trastuzumab combination studies.

Other therapeutic targets for this combination may also be considered. We observed objective responses in esophageal and ovarian cancers, and in two patients with sarcomas. In pursuing phase II studies, since entry is usually restricted to patients with fewer prior therapies than in this phase I study, colony stimulating factors will likely not be required. The current schedule was practical and could be easily administered, even to patients with compromised performance status. In three instances, the patients maintained their initial response with continued administration of Doxil. The absence of cardiac effects makes such a strategy feasible, and documentation of patient benefit through such long-term administration after initial induction with docetaxel and Doxil is an important hypothesis to be tested in phase III trials.

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