A Phase I and Pharmacokinetic Study of CBT-1 as a Multidrug Resistance Modulator in the Treatment of Patients with Advanced Cancer

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CBT-1, a natural product, was studied in an escalating dose Phase I clinical trial with doxorubicin at 60 mg/m^2. CBT-1 was administered by mouth at doses from 200 mg/m^2 to 600 mg/m^2. The drug was given for 7 days and doxorubicin administered intravenously on day 6. The MTD was determined to be 500 mg/m^2 although some patients did tolerate 600 mg/m2 with moderate nausea and occasional vomiting. Side effects were otherwise mild in the 23 patients treated. Pharmacokinetic determinations in an additional 11 patients demonstrated that CBT-1 did not significantly alter the pharmacokinetics of doxorubicin. In this Phase I study, 25 of 34 patients were evaluable for response and 5 patients demonstrated tumor shrinkage.

INTRODUCTION

Chemotherapy is often successful in the initial treatment of patients with advanced solid tumors. Unfortunately, after a period of treatment, sometimes with significant regression of the cancer, growth occurs as a result of acquired drug resistance leading to the subsequent death of the patient. In other solid tumors, inherent drug resistance is believed to be the cause of a lack of sensitivity to most chemotherapy agents. Thus, multi-drug resistance (MDR), whether inherent or acquired, appears to be the major failure mechanism for cancer chemotherapy in patients with advanced cancer.

While a variety of mechanisms of drug resistance are known or postulated, perhaps the best accepted mechanism involves the increased expression of the MDRl gene which encodes the transmembrane glycoprotein Pgp. This mechanism appears to be the basis of resistance to multiple chemotherapy agents including Vinca alkaloids, anthracyclines, epipodophyllo-toxins and taxanes. Pgp is a transmembrane glycoprotein that causes the active effiux of chemotherapy drugs in these classes with reduced intracellular accumulation of the drugs and subsequent drug resistance.

There is now evidence that MDR due to over expression of Pgp can be reversed by several drugs, some of which are now available for clinical use. Initial studies were done with calcium channel blockers such as verapamil. Unfortunately, the plasma levels necessary to achieve reversal of MDR were excessively toxic in patients undergoing clinical trials with these agents. Subsequently, studies with other Pgp modulators such as cyclosporine-A,[11] tamoxifen[12] and PSC-833[13] have been more encouraging. In studies with cyclosporine-A and tamoxifen, MDR related to renal cancer could easily be reversed *in vitro*. Phase I trials determined the appropriate dose that

could be utilized with continuous infusion vinblastine and safely achieve plasma levels consistent with concentrations needed to achieve *in vitro* resistance reversal. Unfortunately, when a Phase II trial was done utilizing either high doses of cyclosporine-A or tamoxifen, no modulation of inherent drug resistance was seen in patients with advanced renal carcinoma treated with continuous infusion vinblastine.[14] In analyzing this study, the authors concluded that neither cyclosporine-A nor tamoxifen was useful in modulating the inherent drug resistance of renal carcinoma to vinblastine. However, Pgp modulation was not measured and the authors felt the randomized trial design was cumbersome and inefficient. Since the modulation of clinical drug resistance is not likely to be useful in the clinic unless the effect is quite substantial, they suggested further Phase II trials with analyses referencing historical controls.[15]

More recent studies using cyclosporine[16] and cyclosporine derivatives such as PSC-833[13] have yielded interesting results. For example, in patients with advanced solid tumors treated with doxorubicin and PSC-833, an oral MDR modulator, a marked pharmacological interaction was noted between the chemotherapy drug and the MDR modulator. This led to significant hematological toxicity and required a reduction in the doxorubicin dose. Although effective modulation was not seen in this study, plasma concentrations that could revert MDR *in vitro* were achieved in patients and further studies are planned with the suggestion that Pgp expression should be measured in the context of those studies.[13, 16]

CBT -1 is a natural product. While its mode of action has not been fully elucidated, experimental data in *in vitro* models demonstrate the drug's activity as an effective modulator of multiple drug resistance. The precise mechanism of action is under investigation, but CBT -1 is felt to modulate Pgp expression, allowing for a greater intracellular accumulation of doxorubicin and the reversal of drug resistance. [17]

This study was the initial Phase I trial to define the tolerable dose range and side effects of CBT -1 when administered with therapeutic doses of doxorubicin. In addition, pharn1acokinetic studies were done of both CBT -1 and doxorubicin during the conduct of this trial. The bioexcretion of CBT –1 was studied by analyzing both the plasma pharmacokinetics and the urine concentrations of CBT -1.

PATIENTS AND METHODS

This was a two-institution Phase I trial conducted with sponsorship of CBA Research, Inc.

Table 1 Patient characteristics	
Characteristic	Value
Total no. of patients	34
Sex (no. of men/no. of women)	14/20
Average age in yrs. (range)	54 (35-76)
Average Karnofsky performance status (range)	78 (50-100)
Tumor type	
Breast	13
Sarcoma	4
Non-small cell lung cancer	4
Colon	4
Ovarian	2
Non-Hodgkin's Lymphoma	3
Hodgkin's Disease	1
Acute Myeloid Leukemia	1
Bladder (transitional cell)	1
Mesothelioma	1
Prior Therapy	
Surgery	28
Radiotherapy	21
Chemotherapy	34
MDR Substrates*	29
Doxorubicin	17

* MDR Substrates included anthracyclines, Vinca alkaloids epipodophyllotoxins, and taxanes

Eligibility Criteria

Patients with advanced solid tumors who were not curable by standard treatment and had failed chemotherapy, usually a doxorubicin-containing regimen, were eligible. Patients were required to have a projected life expectancy of >12 weeks and a Karnofsky performance status of at least 60%.

Normal liver and adequate kidney function (creatinine clearance $\geq$ 50cc per min), normal clotting and stable bone marrow function (white blood count $\geq$ 3000/mm^3, platelet count $\geq$ 100,000/rnm^3) and normal EKGs and an ejection fraction > 45% were required. Women of childbearing age were excluded or had to be on an effective birth control method. Patients with significant coronary artery disease, cardiac arrhythmias or other active cardiac disease were not eligible. Patients were excluded if radiation therapy had been given within one week of entering study or if chemotherapy or other forms of systemic therapy were used within four weeks of entry. Most of the patients were resistant to doxorubicin and must have received a total dose of less than 300 mg/m^2. This study was registered with the Food and Drug Administration and had approval by the institutional review board in each participating institution. Each patient gave informed written consent prior to entering the study. Patient characteristics are shown in Table 1.

Study Design

In the Phase la study, CBT-1 was administered to 23 patients by mouth on days 1- 7 of each 21-day cycle in a dose escalating fashion. Doxorubicin was administered intravenously on day 6 of each cycle at a dose of 60 mg/m2. The dose of

CBT-1 was escalated by cohort with five patients receiving a dose of l00 mg/ m2; three cohorts of three patients each were entered at 200 mg/m^2, 300 mg/nr and 400 mg/m2 respectively. Four patients received 500 mg/m2 and the final cohort of five patients received a dose of 600 mg/m^2.

CBT-1 was supplied by the sponsor, CBA Research Inc., as 50 mg capsules. These capsules were stored in the respective pharmacies at room temperature. Doxorubicin was supplied by each pharmacy. Serum and urine CBT-1 levels were periodically measured, as were the two urinary breakdown products, the N-Z oxide and the N-Z dimethyl products.

In a Phase Ib pharmacokinetic study, 11 patients received 500 mg/m^2 in 7 oral doses in combination with 60 mg/m^2 of doxorubicin on day 6 after an initial cycle of doxorubicin alone, which allowed each patient to serve as his own control. The pharmacokinetics of both CBT-1 and doxorubicin were determined.

In the Phase la portion of the study, patients who were stable or responding at the end of cycle 2 were allowed to remain on treatment for up to six months from the start of therapy. Patients who developed a complete response were to be treated with an additional two cycles and then therapy was to be discontinued. Tumor measurements were performed every two cycles and response definitions were standard with complete response being defined as disappearance of all clinically detectable disease, partial response defined as 50% or greater decrease in the sum of the products of two perpendicular diameters of all measurable disease without an increase in size of any single lesion or the appearance of any new lesions. Progressive disease was defined as greater than a 25% increase of the

Table 2 Dose escalation scheme: patients and courses with doxorubicin in combination with CBT-1™

Dose Level	CBT-1 dose (mg/M²/day)	Doxorubicin Dose mg/M² *	Patients (no.)	Courses
1	100	60	5	14
2	200	60	3	8
3	300	60	3	6
4	400	60	3	6
5	500	60	4**	8
6	600	60	5	12

* Five (5) patients received a reduced dose of doxorubicin beginning in the second cycle of 45mg/M².

** One patient received a reduced dose of CBT-1 during the first cycle.

sum of the products of the two greatest perpendicular diameters or the appearance of new lesions. Stable disease was anything in between partial response and progressive disease. A response was defined to exist if it persisted for at least two cycles. Patients were considered eligible for evaluation of response in this Phase I study if they completed two cycles of treatment.

Patients in the Phase Ib pharmacokinetics study were also allowed to stay on study just as described for the Phase Ia patients.

Pretreatment Evaluations

Prior to treatment, each patient was evaluated by physical examination and appropriate blood and urine tests. A full radiographic evaluation was conducted for measurement of disease and periodic chemical and radiological evaluations were performed to assess the toxicity of the regimen as well as to evaluate the patients for evidence of response.

Dose Modifications

Patients with Grade 3 or 4 toxicity (standard ECOG toxicity criteria were used) had the next cycle delayed until signs and symptoms cleared. Patients with Grade 4 myelo-suppression received the next dose of doxorubicin at a 25% dose reduction. Patients with grade 3 or 4 toxicity thought to be due to CBT-1 received their next dose at 100 mg/m2 less of CBT-1. All such CBT-1 related toxicities were reported to the FDA by the sponsor.

Pharmacokinetics

Samples of venous blood were drawn on day 6 just prior to the doxorubicin dose and then at 0.5, 1.0, 2, 4,8, 12, 18, 24, 36, 48 and 96 hours after the end of the bolus injection. Samples were obtained in heparinized tubes and immediately protected from "light. After centrifugation at 4°C, the plasma supernatant was stored at -20°C until assayed for doxorubicin. During cycle 2, samples were drawn at the same time to determine whether CBT-l administration affected the metabolism or plasma levels of doxorubicin. Therefore, patients served as their own controls. Plasma samples for CBT-l pharmacokinetic analyses were collected prior to the next dose on days I through 7. Urine was collected periodically during cycle 2 and later cycles and examined for the presence of CBT -1 and its two major breakdown products. The pharmacokinetic data were analyzed by the sponsor.

Table 3 Evaluable grade 3 and 4 toxicities by cycle for escalation study

Cohort	CBT-1 level	No. Pts.	No. Cycles	No. Gr. 3 Neutropenia	No. Gr. 4 Neutropenia	No. Febrile Neutropenia	No. Gr. 3/4 Thrombo.	No. Pts. Trans. (RBC)
1	100mg/M^2	5	12	2	0	0	0	0
2	200mg/M^2	3	5	0	4	0	2	0
3	300mg/M^2	3	3	3	0	0	1	0
4	400mg/M^2	3	5	0	3	1	1	0
5	500mg/M^2	4	4	0	2	1	0	0
6	600mg/M^2	5	8	0	4	2	1	2

Table 4 Evaluable grade3/4 toxicities by patient for pharmacokinetics study

	Dox. Dose	No. Pts.	Neutropenia Gr. 3/4	Neutropenic Fever Gr. 3/4	Thrombo. Gr. 3/4	Pts. Rec'd Transfusion
Cycle 1 (Dox. only)	60mg/M^2	11	3	1	2	0
Cycle 2 (CBT-1 & Dox.)	60mg/M^2	7*	4	4	2	3
Cycle 2 (CBT-1 & Dox.)	45mg/M^2	3	3	0	2	1

* 2 pts. treated with dox. only on cycle #3.

Statistics

CBT -I levels were performed by HPLC. As is documented in the results of this paper, the assay is highly reproducible. Data were analyzed by standard statistical tests calculating mean and standard deviation for each cohort of patients.

For the pharmacokinetics of doxorubicin and levels done by HPLC, mean and standard deviations were calculated as shown in the tables.

Shapiro-Wilk and Mann-Whitney U Tests were utilized as is shown in Tables 7 and 8. Calculations of AuC, V_{ss}, MRT and Y terminal ½ lives were done as in previous studies.[16]

RESULTS

The study was successfully conducted with 23 patients entered on the dose-escalating Phase Ia trial. All cohorts were completed and a total of five patients were entered at the highest dose level of 600 mg/m^2 (Table 2). Generally speaking, the CBT-1was well tolerated and the toxicities observed were primarily related to doxorubicin. Peripheral blood cytopenia, particularly neutropenia, was the most significant toxicity observed. Because of the variation in treatment that the patients had previously received, it was difficult to demonstrate a certain, dose response effect on the neutrophil count. However, grade 4 neutropenia was noted primarily in higher dose levels of CBT-1 plus doxorubicin. These data are summarized in Tables 3 and 4. Significant

thrombocytopenia was seen occasionally at all the dose levels, and anemia requiring transfusion was only seen at the highest dose levels of CBT-1.

Hemolysis studies were performed because of previous evidence that CBT-l or its vehicle given intravenously could cause hemolysis. No change in serum haptoglobin or in urine hemosiderin levels was noted. ACTH and cortisol levels were generally within normal range on day 6. Kidney and liver function tests were normal throughout the study.

Gastrointestinal toxicity was observed in one patient each receiving 400 mg/m^2 and 500 mg/m^2 CBT-1. Four of five patients receiving 600 mg/m^2 complained of nausea throughout the 7-day administration with occasional vomiting episodes and infrequent bouts of diarrhea. One patient at 500 mg/m^2 and one patient at 600 mg/m^2 received the 100 mg/m^2 dose reduction of CBT-l due to the nausea.

Mild hypotension was seen at times during the study, as were minor changes in EKG tracings. Two patients had a significant drop in ejection fraction but one of these had a lifetime dose of doxorubicin over 500 mg/m^2. In two patients, mild atrial arrhythmias were noted. All of the cardiac effects seen were felt to be consistent with doxorubicin toxicity rather than CBT-1 effect. Because of the increasing frequency of nausea and occasional vomiting at doses of 600 mg/m^2, a dose of 500 mg/m^2 was felt to be the maximum tolerated dose in this Phase I study.
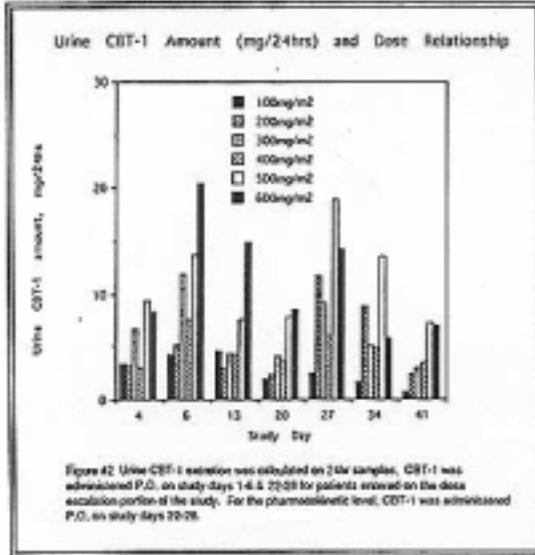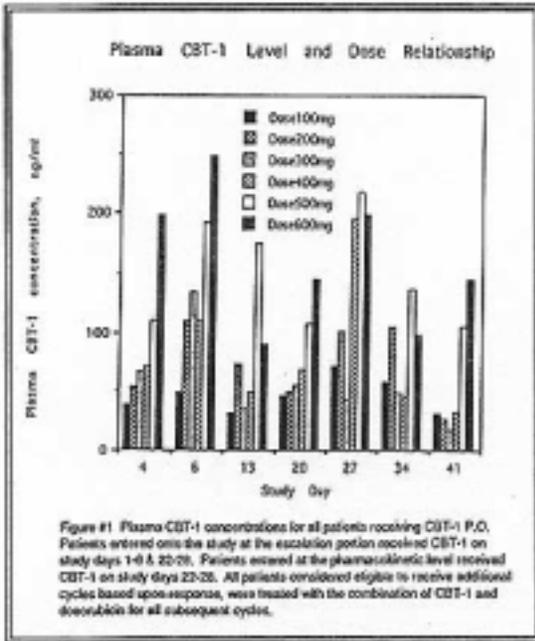
Pharmacokinetics

Eleven patients were entered on the Phase Ib segment of this study at 500 mg/m^2 CBT-1 plus 60 mg/m^2 of doxorubicin. Six patients completed two cycles and one patient each completed 1, 3, 4, 6 or 8 cycles. One patient remained with stable disease throughout the 8 cycles of therapy and one was terminated during treatment for an elevated serum creatinine. Two patients were terminated because they reached the maximum lifetime dose of doxorubicin and one patient had progressive disease. Two patients left to receive alternative therapy and five were discontinued because of progressive disease. Samples for pharmacokinetic analysis were obtained in cycles 1 and 2 from 10 patients.

The toxicities seen in the Phase Ib study was similar to those seen in the Phase Ia study. There were no new toxicities felt to be attributable to CBT-1.

The plasma levels of CBT-1 appeared to be related to dose (Figure 1) and ranged between 12 and 141 nanograms per milliliter to 100 mg/m^2 and from 136 to 347 nanograms per milliliter at 600 mg/m^2 on days 6 and 27 when both CBT-l and doxorubicin were administered. When doses of 500 to 600 mglm^2 were given, the average plasma concentration on days 6 and 27 was well above that necessary (125 mg/ml) to reverse MDR *in vitro* (Table 5). The urine levels of the drug ranged between .29 and 8.3 micrograms per milliliter to 100 mg/m^2 and 1.5 to 26 micrograms/in at 600 mg/m^2 with samples taken on the days 6 and 27 (data not shown). The half-life of the drug is felt to be 5 to 7 days with over 90% of the drug being protein-bound. About 5% of CBT-1 is excreted in the urine in the first 24 hours and most of the excreted drug is unchanged CBT-1. The 24-hour excretion rates are shown in Figure 2.

CBT-1 levels in plasma were determined by HPLC analysis. As can be seen in Tables 6 and 7, the assay is highly reproducible.

Plasma CBT-1 Level and Dose Relationship

Figure #1 Plasma CBT-1 concentrations for all patients receiving CBT-1 P.O. Patients entered onto the study at the escalation portion received CBT-1 on study days 1-6 & 22-28. Patients entered at the pharmacokinetic level received CBT-1 on study days 22-28. All patients considered eligible to receive additional cycles based upon response, were treated with the combination of CBT-1 and doxorubicin for all subsequent cycles.

Urine CBT-1 Amount (mg/24hrs) and Dose Relationship

Figure #2 Urine CBT-1 excretion was calculated on 24hr samples. CBT-1 was administered P.O. on study days 1-6 & 22-28 for patients entered on the dose escalation portion of the study. For the pharmacokinetic level, CBT-1 was administered P.O. on study days 22-28.

dihypodoxorubicin were measured 10 times between 0 and 96 hours post injection, both alone and with CBT -I. These data are shown in tables 8 and 9. Although the area under the curve (AuC) was slightly higher when CBT -I was added, the differences were not significant for doxorubicin or its metabolite.

Antitumor Activity

Of the 34 patients entered in this Phase I study, 26 were evaluable for response assessment. Of those assessed there were 12 with progressive disease, 9 with stable disease, and there were 5 patients with tumor shrinkage (improvement or partial response) seen in the study group. Of the 11 patients in the Phase Ib pharmacokinetics study, 3 remained stable for at least two cycles of therapy. These data are summarized in Tables 10 and 11.

DISCUSSION

CBT-1 plasma levels sufficient to reverse drug resistance *in vitro* were found at most doses above 200 mg/m^2. It is clear from these studies that CBT-1 can be administered orally and adequate plasma levels for MDR modulation are achieved. In addition. unlike cyclosporine and PSC-833, there was no significant alteration in the pharmacokinetics of doxurubicin or its toxicity when the two agents were

Table 5   Plasma levels of CBT-1^{TM} (ng/ml) during dose escalation

CBT-1 Dose mg/M²/day	No. of patients	No. of courses	Plasma Level (ng/ml)	
			t = day 6 $\bar{x}$ (range) ± S.D.	t = day 27 $\bar{x}$ (range) ± S.D.
100	5	13	49.08 (11.79-129.79) 38.40	72.39 (33.72-140.79) 48.77
200	3	8	110.21 (97.51-122.98) 11.45	102.45 (70.50-123.40) 26.12
300	3	6	136.02 (48.90-212.45) 76.54	43.05 (45.19-63.22) 21.32
400	3	6	110.79 (54.57-171.64) 58.67	195.66
500	4	8	192.42 (116.36-379.09) 78.72	218.32 (76.45-379.99) 121.56
600	5	12	248.52 (162.63-347.18) 80.80	199.24 (136.0-230.22) 43.36

Table 6 HPLC analysis of plasma CBT-1™ accuracy, precesion and recovery (intra-assay)

Amount added (ng/ml)	Amount found (ng/ml)	n	S.D.	Deviation (%)	C.V. (%)	Recovery (%)
30	29.91	4	2.61	0.30	8.73	99.70
60	62.08	4	3.13	3.47	5.04	103.47
120	114.88	4	5.43	4.27	4.73	95.73
240	244.22	4	5.59	1.76	2.29	101.76
480	478.92	4	8.40	0.23	1.75	99.78

Table 7 HPLC analysis of plasma CBT-1™ accuracy, precision and recovery (inter-assay)

Amount added (ng/ml)	Amount found (ng/ml)	n	S.D.	Deviation (%)	C.V. (%)	Recovery (%)
30	33.17	8	3.76	10.57	11.34	110.57
60	62.21	8	2.40	3.68	3.86	103.68
120	120.24	8	4.10	0.20	3.41	100.20
240	237.49	8	4.54	1.05	1.91	98.95
480	480.51	8	2.67	0.11	0.55	100.11

Table 8 Doxorubicin summary of analysis and statistics (n=9)

Parameter	Doxorubicin alone				Doxorubicin with CBT-1				Grouped	
	mean	std. dev.	W	prob. <W	mean	std dev.	W	prob. <W	% change	P
AUC normalized	1511.2	803.8	.738	.004	1764.8	483.0	.873	.129	16.78	.231
Clearance (l/hr/M²)	46.76	16.84	.976	.938	33.98	11.81	.907	.288	-27.34	.044
Vss (l/M²)	1856.5	1125.3	.905	.279	1150.4	1081.7	.795	.018	-38.03	.058
MRT (hr)	35.28	24.55	.889	.217	37.19	36.70	.806	.024	5.44	1.00
Terminal 1/2 life (hr)	66.50	68.85	.687	.001	63.42	33.43	.946	.643	-4.63	.906
AUC_{mdox}/AUC_{dox}	1.13	0.43	.744	.005	1.67	1.02	.884	.138	47.05	.155

Note: AUC_{mdox}/AUC_{dox} is a ratio and is therefore without dimensions.

The "W" and "prob. <W" columns refer to the Shapiro-Wilk test which determines the likelihood that the data is normally distributed.

Given a significance level of 0.05, data sets with a P value of less than 0.05 should be considered as different (a significant difference exists).

combined. Therefore, CBT-1 appears to be an excellent agent for further investigation of MDR modulation.

The most frequent toxicity seen in this study was myelosuppression, which was felt to be doxurubicin related. Mild nausea and some vomiting were seen at the 500 and 600 mg/m² dose levels of CBT-l, defining the MTD at 500 mg/m².

Hyperpigmentation was seen in several patients in this study and the other side effects noted were felt to be primarily related to doxorubicin. The lack of significant pharmacological interaction between CBT-1 and doxurubicin is very

Table 9   1,3 dihydrodoxorubicin summary of analysis and statistics   (n=10)

Parameter	1,3 dihydrodoxorubicin alone				1,3 dihydrodoxorubicin with CBT-1				Grouped	
	mean	std. dev.	W	prob. <W	mean	std. dev.	W	prob. <W	% change	P
AUC normalized	1929.6	1254.6	.803	.016	2903.7	1137.3	.748	.004	50.48	.084
Clearance (l/hr/M²)	45.28	30.51	.795	.033	25.91	12.95	.968	.857	-42.77	.002
Vss (l/M²)	1811.6	1003.7	.863	.080	1334.2	969.98	.883	.135	-26.35	.037
MRT (hr)	47.89	24.07	.916	.311	52.19	24.74	.902	.2186	8.98	.808
Terminal 1/2 life (hr)	44.64	21.05	.956	.741	49.44	19.30	.895	.1849	10.73	.895

Note: The "W" and "prob. <W" columns refer to the results of the Shapiro-Wilk test which determines the likelihood that data is normally distributed.

Given a significance level of 0.05, data sets with a P value of less than 0.05 should be considered as different (a significant difference exists).

Table 10   Response Summary Totals For Escalation Study

Diagnosis	Total	Improved*	Stable Disease	Progressive Disease	Inevaluable**
Breast	10	4	1	1	4
Lymphoma	3	1	2	0	0
Sarcoma	4	0	1	1	2
NSCLC	1	0	0	0	1
Colon	2	0	0	2	0
Ovary	2	0	2	0	0
AML	1	0	1	0	0
Totals	23	5	7	4	7

*   Improvement is measurable tumor reduction less than PR and includes two patients with PR

** Patients were considered inevaluable if they were not able to complete two (2) cycles per protocol requirements for assessment.

Table 11   Response Summary Totals For Pharmacokinetics Study

Diagnosis	Total	Improved	Stable Disease	Progressive Disease	Inevaluable
Breast	3	0	2	1	0
NSCL	3	0	0	2	1
Colon	2	0	0	2	0
Bladder	1	0	0	1*	0
Lymphoma	1	0	0	1	0
Mesothelioma	1	0	0	1	0
Totals	11	0	2	8	1

* Stable after two cycles, progressive after four cycles

encouraging. Unlike verapamil, cyclosporine and PSC-833 where clear pharmacokinetic interactions affect the toxicity of chemotherapy, CBT-1 can be administered in tolerable oral doses and plasma levels adequate to modulate MDR effects are achieved without significant changes in the pharmacokinetics of doxorubicin.[13.18-20] Studies of MDR-1 expression and Pgp levels were not done with this Phase I study but are planned in the future.

No neurological side effects were seen with CBT-1, unlike studies with tamoxifen and PSC-833 where significant cerebellar ataxia has been observed.[13.14.21.22]

The antitumor activity seen in 5 of 34 patients with multidrug resistant disease is encouraging. Since oral CBT -I can be given safely with the usual therapeutic dose of doxorubicin and since CBT-1 plasma levels achieved at tolerable doses are consistent with those that will modulate MDR *in vitro,* this drug appears to be a very interesting agent for further evaluation. Studies with CBT-1 are warranted in hematological malignancies and in selected solid tumors where inherent or acquired drug resistance is a therapy limiting problem. In addition, CBT-1 should be studied with other chemotherapy drugs such as the taxanes to evaluate its effects with more recent and more active chemotherapy drugs. Phase la studies of CBT-1 plus taxol have been completed and Phase II studies are m progress.

Not only is it important to study MDR modulators in patients with resistant disease, it will also be important to combine CBT-l with chemotherapeutic agents prior to the development of resistance to determine whether they can increase the response rate to the chemotherapeutic agent and reduce the development of acquired drug resistance during the context of these trials. Such studies may lead to improved response rates and survival times for patients with advanced cancer.

ACKNOWLEDGMENTS

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