Phase I Study of CBT -I™ and Taxol® in Patients with Taxol® Resistant Cancers

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CBT –1™, a natural product, was studied as an MDR modulator with Taxol® (135 mg/M) in an escalating dose Phase I clinical trial.

CBT -1™ was administered orally at doses from 300 mg/m2 to 500 mg/m2 daily x 7. The MTD was determined to be 500 mg/m2 with moderate nausea and occasional emesis. Side effects were previously attributable to Taxol® rather than the study drug. A total of 18 patients were registered on study with only one patient determined to be intolerant of CBT –1™ due to nausea and emesis. In this Phase I study four patients (3 breast, 1 SCLC) remained stable for greater than two cycles of treatment. No complete or partial responses were seen in this Taxofli1 resistant population.

INTRODUCTION

Although the biology and genetics of neoplastic disease are better understood and in spite of the introduction of many new treatments, cancer remains predominantly a progressive and fatal disease in its metastatic phase.

Chemotherapy is often initially successful in the treatment of patients with advanced solid tumors. Unfortunately, after a period of treatment, growth occurs as a result of acquired drug resistance leading to the subsequent death of the patient. In other solid tumors, de novo 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, epipodophyllotoxins and taxanes. Pgp is a transmembrane glycoprotein that causes the active eft1ux of chemotherapy drugs in these classes with reduced intracellular accumulation of the drugs and subsequent drug resistance.[1-9]

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There is now evidence that MDR due to overexpression of Pgp can be reversed by several drugs, termed MDR modulators, some of which are now available for clinical use. Initial studies were done with calcium channel blockers such as verapamil.[10] Unfortunately, the plasma levels necessary to achieve reversal of MDR were excessively toxic in patients undergoing initial clinical trials with these agents.[11] Subsequently, studies with other Pgp modulators such as cyclosporine-A,[12] tamoxifen[13] and PSC-833[14] have been more encouraging.[15-19] 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 to 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.[20] 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.[21]

More recent studies using cyclosporine[22] and cyclosporine derivatives such as PSC-833[14] 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. A recent study of PSC-833 in acute myeloid leukemia utilized the modulator with reduced chemotherapy doses.[23] Although modulation was not measured 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.[23]

CBT-1™ is a natural product. While its mode of action has not been fully elucidated, experimental data with in vitro models demonstrated the drug's activity as an effective modulator of multiple drug resistance. CBT-1™ is felt to modulate Pgp expression, allowing for a greater intracellular accumulation of drugs and the reversal of drug resistance.[24]

This study was the second Phase I trial to define the tolerable dose range and side effects of CBT-1™ when administered with chemotherapy. The initial study was done with doxorubicin25 and this study was conducted with Taxol®. In addition, pharmacokinetic studies were done of CBT-1™, doxorubicin and Taxol® during the conduct of the initial trial.

PATIENTS AND METHODS

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

Eligibility Criteria

Patients with advanced solid tumors who were not curable by standard treatment and had failed a Taxol® containing regimen, were eligible. Patients were required to have a projected life

expectancy of > 12 weeks and a Kamofsky 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/mm3, platelet count $\geq$ 100,000/mm3) and normal EKGs 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 three weeks of entry. All of the patients were resistant to Taxol®. 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 I.

Study Design

In this Phase I study, CBT –1™ was to be administered to 18 patients by mouth on days 1-7 of each 21-day cycle in a dose escalating fashion. Taxol® was administered intravenously on day 6 of each cycle at a dose of 135 mg/m^2 .The dose of CBT –1™ was escalated by cohort with six patients to receive a dose of 300 mg/ m^2; seven patients 400 mg/m^2 and the final cohort of five patients to receive a dose of 500 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. Taxol® was supplied by each pharmacy. In selected patients, serum and urine CBT –1™ levels were periodically measured.

In this 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 within six months 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 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 or stable disease was defined to exist if it persisted for at least two cycles. All registered patients, even if never treated, were included in this analysis. Patients were considered eligible for evaluation of response in this Phase I study if they completed two cycles of treatment.

Pretreatment Evaluation

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 myelosuppression received the next dose of Taxol® 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/m^2 less of CBT-1™. All such CBT-1™ related toxicities were reported to the FDA by the sponsor .

Statistics

CBT–1™ levels were performed by HPLC. As is documented in a previous paper, the assay is highly reproducible.[25] Data were analyzed by standard statistical tests calculating mean and standard deviation for each cohort of patients.

RESULTS

The study was successfully conducted with 18 patients registered on the dose-escalating Phase I trial. Three (3) patients did not complete cycle 1 due to disease progression. Two (2) patients received a single cycle and 13 received 2 or more cycles. All cohorts were completed and a total of five patients were treated at the highest dose level of 500 mg/m^2 (Table 2). Generally speaking, the CBT–1™ was well tolerated and the toxicities observed were primarily related to Taxol®. Toxicity was evaluated in all patients receiving at least one dose of CBT–1™. Peripheral blood cytopenia, particularly neutropenia, was the most significant toxicity observed. These data are summarized in Table 3. Significant thrombocytopenia and anemia was seen occasionally.

Hemolysis studies were performed because of some previous evidence that CBT–1™ or its vehicle given intravenously could cause hemolysis. No change in serum haptoglobin or in urine hemosiderin levels were 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 felt to be drug related in one patient each receiving 300 mg/m^2 and 400 mg/m^2 CBT–1™. Of the 5 patients who did not complete the two cycles, 4 had nausea but all had disease complications felt to be the cause of their gastrointestinal signs. The 5 patients receiving 500 mg/m2 had no complaints of nausea.

Because of the increasing frequency of nausea and occasional vomiting at doses of 600 mg/m^2 in the earlier Phase I study, the study was terminated at 500 mg/m2 in this study.

Antitumor Activity

Of the 18 patients entered in this Phase I study, 13 received at least 2 cycles of treatment and were evaluable for response assessment. Of those assessed there were 9 with progressive disease and 4 with stable disease. These data are summarized in Table 5.

DISCUSSION

CBT–1™ plasma levels sufficient to reverse drug resistance in vitro were found at doses above 200 mg/m2 in this study and the previous Phase I study .[25] 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 pham1acokinetics of Taxol® (unpublished data) and doxorubicin25 or their toxicities when used with CBT–1™. Therefore, CBT–1™ appears to be an excellent drug for further investigation of MDR modulation.

The most frequent toxicity seen in this study was myelosuppression, which was felt to be Taxol® related. Mild nausea and some vomiting were seen at the 300 and 400 mg/m2 dose levels of CBT–1™ .

CBT–1™ hyperpigmentation was seen in several patients in this study but the other side effects noted were felt to be primarily related to Taxol® or the disease. The lack of significant pham1acological interaction between CBT -I"' and doxurubicin or Taxol® is very encouraging. Unlike veraparnil, 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 and Taxol®.[14,26-28] 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. [14,20,29,30]

The antitumor activity seen in 4 of 13 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 -I"' 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 Phase II/III evaluation.

Not only is it important to study MDR modulators in patients with resistant disease, it will also be important to combine CBT–1™ 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.[31] Such studies may lead to improved response rates and survival times for patients with advanced cancer.

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