METHOD AND COMPOSITIONS FOR ADMINISTERING TAXANES ORALLY TO HUMAN PATIENTS

FIELD OF THE INVENTION

The invention relates to methods and compositions for orally administering to humans pharmaceutical agents that are poorly absorbed from the gastrointestinal tract, and to methods of treatment of patients through the oral administration of such agents. More particularly, the present invention relates to methods and compositions for orally administering paclitaxel and related taxanes to humans.

BACKGROUND OF THE INVENTION

Many valuable pharmacologically active compounds cannot be effectively administered by the oral route to human patients because of poor or inconsistent systemic absorption from the gastrointestinal tract. All these pharmaceutical agents are, therefore, generally administered via intravenous routes, requiring intervention by a physician or other health care professional, entailing considerable discomfort and potential local trauma to the patient and even requiring administration in a hospital setting with surgical access in the case of certain intravenous (i.v.) infusions.

One of the important classes of cytotoxic agents which are not normally bioavailable when administered orally to humans are the taxanes, which include paclitaxel, its derivatives and analogs. Paclitaxel (currently marketed as TAXOL® by Bristol-Meyers Squibb Oncology Division) is a natural diterpene product isolated from the pacific yew tree (*Taxus brevifolia*). It is a member of the taxane family of terpenes. It was first isolated in 1971 by Wani *et al.*, (J. Am. Chem. Soc., *93*:2325, 1971), who characterized its structure by chemical and X-ray crystallographic methods. One mechanism for its activity relates to the capacity of paclitaxel to bind tubulin, thereby inhibiting cancer cell

growth. Schiff *et al.*, Proc. Natl. Acad. Sci. USA, 77:1561-1565 (1980); Schiff *et al.*, Nature, *277*:665-667 (1979); Kuman, J. Biol. Chem., *256*:10435-10441 (1981).

Paclitaxel has been approved for clinical use in the treatment of refractory ovarian cancer in the United States (Markman *et al.*, Yale Journal of Biology and Medicine, *64*: 583, 1991; McGuire *et al.*, Ann. Intern. Med., *111*:273, 1989). It is effective for chemotherapy for several types of neoplasms including breast (Holmes *et al.*, J. Nat. Cancer Inst., *83*:1797, 1991) and has been approved for treatment of breast cancer as well. It is a potential candidate for treatment of neoplasms in the skin, lung cancer and head and neck carcinomas (Forastire *et al.*, Sem. Oncol., *20*:56, 1990). The compound also shows potential for the treatment of polycystic kidney disease (Woo *et al.*, Nature, *368*:750, 1994) and malaria.

The poor solubility of paclitaxel in water has created significant problems in developing suitable injectable and infusion formulations useful for anticancer chemotherapy. To improve the solubility of paclitaxel in aqueous solutions, some paclitaxel compositions formulated for IV infusion have included CREMOPHOR® EL (a condensation product of polyethoxylated castor oil and ethylene oxide sold by BASF). For example, paclitaxel used in clinical testing under the aegis of the National Cancer Institute (NCI) has been formulated in 50% CREMOPHOR® EL and 50% dehydrated alcohol. CREMOPHOR® EL has proven to be toxic and to produce vasodilation, labored breathing, lethargy, hypotension and death in dogs following IV administration. It is also believed to cause allergic-type or hypersensitivity reactions. Evidence also exists that paclitaxel itself provokes acute hypersensitivity reactions in the absence of CREMOPHOR® EL.

Paclitaxel analogs derivatized at the 2' and/or 7-positions with groups that enhance water solubility have been

synthesized. These efforts have yielded prodrug compounds that are more water soluble than the parent compound and that display the cytotoxic properties upon activation. One important group of such prodrugs includes the 2'-onium salts of paclitaxel and docetaxel, particularly the 2'-methylpyridinium mesylate (2'-MPM) salts.

Animal studies have demonstrated that paclitaxel is very poorly absorbed when administered orally (less than 1%). See Eiseman, *et al.*, Second NCI Workshop on Taxol and Taxus (Sept. 1992); Suffness *et al.*, in Taxol Science and Applications (CRC Press 1995). Eiseman, *et al.*, indicate that paclitaxel has a bioavailability of 0% upon oral administration, and Suffness, *et al.*, report that oral dosing with paclitaxel did not seem possible because no evidence of antitumor activity was found on oral administration up to 160 mg/kg/day.

In PCT application WO 95/20980 (published August 10, 1995), Benet, *et al.*, disclose a purported method for increasing the bioavailability of orally administered hydrophobic pharmaceutical compounds. This method comprises orally administering such compounds to the patient concurrently with a bioenhancer comprising an inhibitor of a cytochrome P450 3A enzyme or an inhibitor of P-glycoprotein-mediated membrane transport. Benet, *et al.*, however, provide virtually no means of identifying which bioavailability enhancing agents will improve the availability of specific "target" pharmaceutical compounds, nor does it indicate specific dosage amounts, schedules or regimens for administration of the enhancing or target agents. Benet lists dozens of potential enhancers (P450 3A inhibitors) and target drugs (P450 3A substrates) but the only combination of enhancer and target agent exemplified in terms of experimental evidence is ketoconazole as the enhancer and cyclosporin A as the target drug.

Thus, a need remains for methods of administering taxanes, *e.g.*, paclitaxel which are cytotoxic compounds, that are safe and effective, and particularly methods that reduce adverse reactions associated with parenteral administration of paclitaxel and various solubilizers and excipients such as CREMOPHOR® EL.

SUMMARY OF THE INVENTION

One aspect of the present invention is directed to a method of reducing incidence or severity of hypersensitivity reactions associated with parenteral administration of a taxane. The method entails orally administering a taxane formulation wherein the formulation causes hypersensitivity reactions when administered parenterally. In preferred embodiments, the taxane is selected from the group of paclitaxel, docetaxel, a derivative, analog, or prodrug of paclitaxel or docetaxel *e.g.*, paclitaxel-2'MPM and docetaxel-2'-MPM, taxane 2'MPM salts and polymorphs and hydrates thereof. It is preferred that the taxane is present in the formulation in an amount from about 60 mg/m^2 to about 250 mg/m^2.

Applicants have also discovered that the gut is substantially impervious to orally administered CREMOPHOR® EL. That is, cremophor is not transported across the gut epithelia to achieve detectable levels in blood. Accordingly, another aspect of the present invention is directed to a method of selectively enhancing the bioavailability of a pharmaceutically active agent. The method involves orally co-administering to a human a bioavailability enhancing agent and a formulation including a pharmaceutically active agent and at least one solvent. Preferred bioavailability enhancing agents include cyclosporins A-Z, dihydrocyclosporin A, dihydrocyclosporin C, acetyl cyclosporin A, PSC-833 and SDZ-NIM 811. The pharmaceutical agent achieves therapeutic blood levels but the solvent that tends to cause the adverse side

reactions such as hypersensitivity does not achieve active blood levels. In preferred embodiments, the pharmaceutical agent is a taxane and the solvent is a polyalkoxylated castor oil such as CREMOPHOR® EL. In more preferred embodiments, the CREMOPHOR is present in the formulation in an amount from about 3 to about 10 mg/ml.

A further aspect of the present invention is directed to a composition containing a taxane and a polyalkoxylated castor oil (optimally including an excipient) in the form of an oral dosage unit.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph reflecting the circulating levels of paclitaxel in samples taken: (a) lower curve - over a period of 6-8 hours from one group of rats administered only oral paclitaxel, and (b) upper curve - over a period of 24 hours from a second group of rats administered orally one hour prior to the co-administration of oral cyclosporin A and oral paclitaxel.

FIG. 2 is a graph reflecting the levels of paclitaxel in plasma samples from a human patient administered oral paclitaxel after two dose of oral cyclosporin A, the first administered one hour before the paclitaxel dose and the second administered immediately before the paclitaxel.

FIG. 3 is a graph reflecting the levels of paclitaxel in plasma samples from a second human patient administered oral paclitaxel by the same regimen as described with respect to FIG. 2.

FIG. 4 is a graph reflecting a comparison of the paclitaxel plasma level curves determined over 24 hours in rats (FIG. 1) and in humans (FIGS. 2 and 3) administered oral paclitaxel after two doses of oral cyclosporin A.

FIG. 5 is a table reflecting treatment schedule of oral paclitaxel and cyclosporin used in Example 5.

FIG.6 is a table reflecting the hematologic toxicity after oral administration of paclitaxel described in Example 5.

FIGS.7A and 7B are tables reflecting the non-hematologic toxicity after oral administration of paclitaxel described in Example 5.

FIG.8 is a table reflecting the pharmacokinetics of oral paclitaxel described in Example 5.

FIG.9 is a table reflecting the pharmacokinetics of CsA described in Example 5.

FIG. 10 is a graph reflecting the area under the curve (AUC, (uM.h)) of oral paclitaxel versus dose (mg/m^2).

DETAILED DESCRIPTION OF THE INVENTION

A first aspect of the present invention provides a method of preventing or reducing hypersensitivity and allergic reactions in human patients receiving taxane therapy. The method comprises the oral administration of the taxane to the patients. Oral administration by the instantly disclosed method is much less likely than intravenous therapy to produce such adverse reactions. Applicants administered paclitaxel to human patients (see Examples 2 and 3) with no pre-medication (*e.g.*, no H-1 H-2 blockers or steroids). Therapeutic circulating levels of paclitaxel were achieved and no hypersensitivity reactions were observed.

Applicants have discovered that the taxanes, which have been believed to be characterized by therapeutically inadequate oral absorption profiles, can be administered orally to humans with sufficient systemic absorption and oral bioavailability achieved to exhibit plasma levels in the therapeutic range. The term "bioavailability" as used herein refers to the systemic availability (i.e., blood/plasma levels) of a given amount of drug administered to a patient. Applicants have actually administered the taxane paclitaxel orally to human patients suffering from cancers and have

verified that therapeutic blood levels of paclitaxel were achieved in these patients over extended periods of time.

In a preferred embodiment, the taxane is co-administered with an absorption or bioavailability enhancing agent to a human patient. "Co-administration" of the enhancing agent comprehends administration substantially simultaneously with the taxane (either less than 0.5 hr. before, less than 0.5 hr. after or together), from about 0.5 to about 72 hr. before the administration of the taxane, or both, *i.e.*, with one or more doses of the same or different enhancing agents given at least 0.5 hr. before and one dose given substantially simultaneously with (either together with or immediately before or after) the taxane. Additionally, "co-administration" comprehends administering more than one dose of taxane within 72 hr. after a dose of enhancing agent, in other words, the enhancing agent(s) need not be administered again before or with every administration of taxane but may be administered intermittently during the course of treatment.

The orally administered enhancing agents useful in practicing the preferred embodiment of the invention include, but are not limited to cyclosporins, including cyclosporins A through Z but particularly cyclosporin A (cyclosporin), cyclosporin F, cyclosporin D, dihydro cyclosporin A, dihydro cyclosporin C, acetyl cyclosporin A, PSC-833, and SDZ-NIM 811 *i.e.*, ((Me-Ile-4)-cyclosporin, an antiviral, non-immunosuppressive cyclosporin)(both available from Novartis Pharmaceutical Corp). The structures of cyclosporins A-Z are described in Table 1 below.

TABLE 1

Cyclosporins A-Z

Cyclosporin	Aminoacids										
Cy-	1	2	3	4	5	6	7	8	9	10	11
CyA	Mebmt	Abu	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyB	Mebmt	Ala	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyC	Mebmt	Thr	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyD	Mebmt	Val	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyE	Mebmt	Abu	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	Val
CyF	Desoxy Mebmt	Abu	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyG	Mebmt	Nva	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyH	Mebmt	Abu	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyI	Mebmt	Val	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyK	Desoxy Mebmt	Val	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyL	Bmt	Abu	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyM	Mebmt	Nva	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyN	Mebmt	Nva	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	Leu	MeVal
CyO	MeLeu	Nva	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyP	Bmt	Thr	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyQ	Mebmt	Abu	Sar	Val	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyR	Mebmt	Abu	Sar	MeLeu	Val	Leu	Ala	D-Ala	MeLeu	Leu	MeVal
CyS	Mebmt	Thr	Sar	Val	Val	MLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyT	Mebmt	Abu	Sar	MeLeu	Val	Meleu	Ala	D-Ala	Meleu	Leu	MeVal
CyU	Mebmt	Abu	Sar	MeLeu	Val	Leu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyV	Mebmt	Abu	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal
CyW	Mebmt	Thr	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	Val
CyX	Mebmt	Nva	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	Leu	MeLeu	MeVal
CyY	Mebmt	Nva	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	Leu	MeLeu	MeVal
CyZ	Me Amino Octyl acid	Abu	Sar	MeLeu	Val	MeLeu	Ala	D-Ala	MeLeu	MeLeu	MeVal

Cyclosporins are neutral, lipophilic, cyclic undecapeptides with molecular weights of about 1200, and that exhibit immunosuppressive properties. They are produced by the members of the genus *Topycladium*, including *e.g.*, *Topycladium inflatum Gams* (formerly designated as *Trichoderma polysporum*), *Topycladium terricola* and other fungi imperfecti. The major component is cyclosporin A, also referred to as cyclosporine or CsA. several other lesser metabolites, including cyclosporins B through Z, have been found to exhibit substantially less immunosuppressive activity than cyclosporin A, or in some cases, no immunosuppressive activity. They are used intravenously or orally as immunosuppressants, primarily for organ transplantation and certain other conditions. Cyclosporins, particularly cyclosporin A, are known inhibitors of the P-glycoprotein efflux pump and other transporter pumps as well as of certain cytochrome P450 degradative enzymes, but to date no effective regimens for applying this property clinically have been developed to the point of clinical and commercial feasibility or regulatory approval. A number of synthetic and semi-synthetic analogs have been prepared. See generally Jegorov, *et al.*, Phytochemistry *38*:403-407 (1995). Natural, semi-synthetic and synthetic analogs of cyclosporins may be used in the practice of the present invention.

The cyclosporin may be chosen without regard as to whether it exhibits immunosuppressive activity *in vivo*. One of the surprising discoveries of the invention is that the immunosuppression observed with certain cyclosporins is not inextricably linked to improvement in oral bioavailability of therapeutic agents. Thus, cyclosporin F enhances the oral bioavailability of paclitaxel even though it has been reported not to display immunosuppresive activity. Stewart, *et al.*, Transplantation Proceedings *20*(Supp. 3):989-992 (1998); Granelli-Piperno, *et al.*, Transplantation *46*: 53S-60S (1988).

Without intending to be bound by any particular theory of operation, a possible explanation for the observed increased bioavailability of paclitaxel is that there is interaction at the level of the drug metabolizing enzymes for cyclosporine and paclitaxel. It is known that both agents are highly metabolized by the cytochrome P-450 system (*e.g.*, P-450 3A), which is concentrated in the liver as well as the small intestine. It is conceivable that cyclosporine administered prior to the taxane inhibits these enzymes so that paclitaxel, which is non-polar and lipophilic, is absorbed. In the absence of this local inhibition, paclitaxel is metabolized to more polar metabolites that do not transverse the mucosa.

This theorized inhibition of gut metabolism of the target agent might have little or no effect in increasing systemic blood levels when the target agent is administered intravenously. Moreover, since the primary effect of the oral absorption-enhancing agent may be a local effect in the gut lumen, doses which are sub-therapeutic (*e.g.*, in terms of immunosuppression) should be effective in achieving the desired effect. This is an important consideration in the case of enhancing agents such as cyclosporins that have powerful immunosuppressive activity and can present toxicity problems if administered at high dose levels. Thus, Applicants' observation that non-immunosuppressive cyclosporins, such as cyclosporin F, can still function as an oral enhancer is of great clinical value.

The term "taxane" includes but is not limited to paclitaxel, paclitaxel analogs such as docetaxel (N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyl paclitaxel), derivatives, analogs and prodrugs of paclitaxel and docetaxel *e.g.*, salts such as paclitaxel-2' methylpyridinium (MPM) and docetaxel-2'-MPM, taxane 2'MPM salts, and polymorphs and hydrates thereof. The dosage range of orally administered taxane target agents will vary from compound to compound based on its therapeutic index, the requirements of the condition being treated, the

status of the patient and so forth. The method of the invention makes it possible to administer paclitaxel and other taxanes orally ranging from about 20 mg/m^2 to about 1000 mg/m^2 (based on patient body surface area) or about 2-30 mg/kg (based on patient body weight) as single or divided (2-4) daily doses, and maintain the plasma levels of paclitaxel in humans in the range of 50-500 ng/ml for extended periods of time (*e.g.*, 8-12 hours) after each oral dose. These levels are at least comparable to those achieved with 96-hour IV infusion taxol therapy (which causes the patient great inconvenience, discomfort, loss of quality time, infection potential, etc.). Moreover, such plasma levels of paclitaxel are more than sufficient to provide the desired pharmacological activities of the target drug, *e.g.*, inhibition of tubulin disassembly (which occurs at levels of abut 0.1 μM, or about 85 ng/ml) and inhibition of protein isoprenylation (which occurs at levels of about 0.03 μM, or about 25 ng/ml) which are directly related to its antitumor effects by inhibiting oncogene functions and other signal-transducing proteins that play a pivotal role in cell growth regulation. The tumor does not distinguish how the anti-cancer drug was administered.

Preferred oral dosage amounts for paclitaxel and other taxanes administered according to the invention are about 60-250mg/m^2 or about 2-6 mg/kg. It may be suitable in some instances to administer to the patient a higher initial loading dose of the target agent to achieve peak blood levels, followed by lower maintenance doses.

The dosage range of the enhancing agent co-administered with the taxane in accordance with the invention is about 0.1 to about 20 mg/kg of patient body weight. Two or more different enhancing agents and/or two or more different target agents may be administered together, alternately or intermittently in all of the various aspects of the method of the invention.

The present invention may be employed to treat human patients afflicted with cancers, tumors, Kaposi's sarcoma, malignancies, uncontrolled tissue or cellular proliferation secondary to tissue injury, and any other disease conditions responsive to taxanes. Among the types of carcinoma that may be treated particularly effectively are hepatocellular carcinoma and liver metastases, cancers of the gastrointestinal tract, pancreas, prostate and lung, and Kaposi's sarcoma. Examples of non-cancerous disease conditions which may be effectively treated with these active agents administered orally in accordance with the present invention are uncontrolled tissue or cellular proliferation secondary to tissue injury, polycystic kidney disease, inflammatory diseases (*e.g.*, arthritis) and malaria, including choroquine- and pyrimethamine-resistant malaria parasites. See, Pouvelle, *et al.*, J. Clin. Invest. 44:413-417 (1994).

The invention is particularly useful in the treatment of patients with primary tumors and metastases. The active ingredient penetrates the gut wall as a result of the co-administration of the cyclosporin enhancer and is taken up by the portal circulation rapidly, providing a higher local initial concentration of the chemotherapeutic agent in the liver. This local concentration may in fact be higher than the concentration currently achieved with IV infusion therapy). Higher levels of paclitaxel in the liver after oral administration may not be reflected in increased plasma levels because of the high first pass effect of the liver. The method of the invention, in selectively producing high blood concentrations of antitumor agents, is particularly valuable in the treatment of liver cancers (*e.g.*, hepatocellular carcinoma and liver metastases), gastrointestinal cancers (*e.g.*, colon, rectal) and lung cancers.

It is emphasized that this aspect of the present invention does not require any particular bioavailability enhancing agent. Nor is it restricted to any specific dosage

amounts or regimens. In less preferred embodiments, the taxane is administered without a bioavailability enhancing agent.

Another aspect of the present invention is directed to a composition containing a taxane in the form of an oral dosage unit. The dosage unit may be in the form of conventional tablets, capsules (soft gel or hard gel), caplets, gel caps, pills, liquids (*e.g.*, solutions, suspensions or elixirs), powders, lozenges, micronized particles or osmotic delivery systems and any other oral dosage forms known in the pharmaceutical arts. In preferred embodiments, the dosage unit is in the form of a liquid and includes paclitaxel or other taxane in a vehicle comprising CREMOPHOR® EL or other polyalkoxylated castor oil (*e.g.*, a polyethoxylated castor oil), alcohol and/or a polyoxyethylated sorbitan mono-oleate (*e.g.*, TWEEN® 80, ICI Americas, Inc.), transcutol and optionally a flavorant. Each dosage unit includes an effective amount of a taxane and a carrier. The carrier may contain one or more of the following ingredients, namely vehicles, fillers, binders or excipients, disintegrants, solvents, sweeteners, coloring agents and any other inert ingredients which are regularly included in pharmaceutical dosage forms for oral administration. See, *Remington's Pharmaceutical Sciences*, 17th edition (1985).

Precise amounts of each of the taxane in the oral dosage forms will vary depending on the age, weight, disease and condition of the patient. For example, paclitaxel or other taxane dosage forms may contain sufficient quantities of the target agent to provide a daily dosage of about 20-1000 mg/m^2 (based on patient body surface area) or about 2-30 mg/kg. mg/kg (based on patient body weight) as single or divided (2-3) daily doses. Preferred dosage amounts are about 50-200 mg/m^2 or about 2-6 mg/kg.

Dosing schedules will also vary depending on factors such as the patient's characteristics and disease status.

Preferred dosing schedules for administration of oral paclitaxel are (a) the daily administration to a patient in need thereof of 1-4 equally divided doses providing about 20-1000 mg/m^2 (based on body surface area), and preferably about 50-200 mg/m^2, with the daily administration being continued for 1-4 consecutive days each 2-3 weeks, or (b) administration for about one day each week. The former schedule is comparable to use of a 96-hour paclitaxel infusion every 2-3 weeks, which is considered by some a preferred IV treatment regimen.

Oral administration of taxanes in accordance with the invention actually decreases toxic side effects in many cases as compared with currently utilized IV therapies. Without intending to be bound by theory, Applicants believe that as opposed to IV infusion which produces a sudden and rapid high concentration in blood levels, oral administration results in absorption of the active agent through the gut wall (promoted by the enhancing agents), a more gradual appearance in the blood levels and a stable, steady-state maintenance of those levels at or close to the ideal range for a long period of time.

The plasma levels of the taxanes administered in accordance with preferred embodiments of the present invention are remarkably and surprisingly similar to the levels observed following IV administration. A series of studies with experimental animals showed that steady state plasma levels of paclitaxel were achieved upon oral co-administration with CsA by the third day of the regimen. The levels of the target agent achieved at steady state were comparable to those achieved in patients by a 96-hour IV infusion of paclitaxel. A 27% response rate was found in patients with metastatic breast cancer treated with a continuous 96-hour infusion every three weeks (Siedman *et al.*, J. Clin Oncol., *14*:1877, 1996) who had previously failed 3-hour infusions of taxane (taxol or taxotene). Comparable blood level results can be achieved with

the treatment methods of the present invention without the discomfort, inconvenience and risks of prolonged IV infusions.

The data reflected in FIGS. 1-4 are especially noteworthy in view of the surprising nature of the results. As described in more detail in the Examples set forth below, the data reflected in FIG. 1 were generated from studies of paclitaxel administration to rats, but the data reflected in FIGS. 2 and 3 reflect actual concentration levels of paclitaxel over time in the plasma of two human patients administered oral paclitaxel in accordance with the present invention, i.e., with co-administration of an oral cyclosporin enhancing agent. The human data are remarkable not merely because they reflect for the first time, to the extent found in the literature, that paclitaxel was administered orally to human beings requiring paclitaxel therapy, but also because therapeutic-level plasma concentrations were achieved and maintained over about a 10-hour period; indeed, the level of drug seen in the plasma of the human patients were comparable to the levels achieved upon IV administration and the methods used did not bring about serious local or systemic side effects. Furthermore, it should be noted that plasma levels are a reflection of the concentration of paclitaxel in tissue.

It has now been demonstrated that the rat pharmacokinetic profile of paclitaxel co-administered with oral cyclosporin A is quite comparable to the profile in human patients receiving the same regimen. Indeed, FIG. 4 reflects a superimposition on the same graph of the plasma concentration curves for paclitaxel over a 24-hour period following oral co-administration of two doses of enhancer (cyclosporin A) spaced on hour apart with oral paclitaxel administered after the second dose of enhancer (cyclosporin A) spaced one hour apart with oral paclitaxel administered after the second dose of enhancer, said data being derived from the 24-hour rat study reflected in FIG. 1 and the studies on human patients reflected in FIGS 2 and 3. It may be observed that the three curves on the graph in FIG. 4 (one rat and two

human) are of very similar configuration, indicating that the results in human are consistent with the animal test results.

The rat is an accepted model for assessing the pharmacokinetics and absorption profiles of chemotherapeutic agents. It is equally well established, however, that results in animals are not predictive of results in humans due to known species-to-species variations. Thus, no clinician or medical practitioner would have administered paclitaxel or other taxanes orally to humans with reasonable confidence based on the animal data alone without any human clinical experience. Furthermore, doctors are unlikely to experiment with drugs in life-threatening conditions, *i.e.*, cancer, when data are unavailable. The present invention, therefore, teaches a method whereby taxanes can be orally administered safely and effectively to humans. From the standpoint of a physician, the current invention is a vast improvement over the prior art because it allows for the utilization of the beneficial properties of a taxane such as paclitaxel without the necessity of intravenous catheters and time spent in a hospital or chemotherapy clinic, as well as the availability of a clinic and the attendant expense, inconvenience and risk of infection to the patient, pre-medication to avoid hypersensitivity or allergic reactions, and potential adverse effects from the pre-medications themselves.

Paclitaxel use is associated with a variety of toxicities and side effects. Two of the most noteworthy toxicities are neutropenia and neuropathy. A variety of clinical data have shown that it would be desirable to keep the circulating plasma concentrations within a certain "window" in order to maximize the anti-tumor activity and minimize the side effects, especially neutropenia. For many tumor types, it is believed that low, but long-term exposure of tumor cells in the body results in better clinical results. Thus, plasma levels of about .03 micromolar would be expected to block cell division. There are clinical data showing that constant intravenous administration over several days to

achieve a "window" of about 0.05 to 0.1 micromolar in the circulation can minimize toxicities and cause tumor regressions, sometimes even in patients whose tumors did not respond to 3-hour infusion regimens. The currently approved 3-hour infusion regimens of paclitaxel achieve peak plasma concentrations that greatly exceed these levels.

The present invention makes it possible to give paclitaxel in comparatively infrequent daily doses (*e.g.*, about twice/day) according to schedules that would otherwise not be possible or practical with the intravenous route. The use of the enhancer (*e.g.*, cyclosporin A) promotes oral absorption of paclitaxel for the first dose and if a second paclitaxel dose is to be given later in the day, the use of additional cyclosporin A may not even be needed. Thus, paclitaxel can be given intermittently as single dose on a fixed schedule (weekly, biweekly, etc.) or chronically, over a period of consecutive days (*e.g.*, 4 days) every 2-4 weeks with the goal of keeping the levels within the safe and effective "window" and reducing the toxicities discussed above.

Another aspect of the invention is directed to a method of selectively enhancing the bioavailability of a taxane or other pharmaceutical agent. The method entails orally co-administering to a patient a bioavailability enhancing agent and a formulation containing the pharmaceutical agent and a solvent. The pharmaceutical agent achieves therapeutic blood levels but the solvent is not absorbed. Because of its physico-chemical properties, paclitaxel has been typically dissolved in Cremophor for IV administration. The speculation has been that Cremophor is responsible for some of the allergic-type reactions experienced by patients receiving paclitaxel therapy. As a result, patients are pre-medicated to avoid or reduce hypersensitivity reactions. Paclitaxel must be given slowly to patients, with medical personnel in a state of constant vigilance for severe hypersensitivity reactions. For standard

intravenous regimens, pre-medication regimens of H-1 and H-2 blockers plus steroids are generally required.

Applicants have discovered that oral co-administration of a bioavailability enhancing agent and a taxane formulation containing the taxane, CREMOPHOR® EL and ethanol results in uptake of the taxane to achieve pharmacologically effective or therapeutic blood levels with no appreciable blood level of the Cremophor so as to cause adverse side effects. Accordingly, this aspect of the present invention embraces the use of any pharmaceutical agent that is soluble in a solvent such as a polyalkoxylated castor oil that tends to cause adverse side effects such as hypersensitivity reactions when administered parenterally. The enhancing agent facilitates uptake or absorption of the pharmaceutically active agent through the gut but it does not exert this action with respect to the solvent.

Taxanes are preferred active agents. Other agents include antineoplastic drugs such as chemotherapeutic agents (*e.g.*, etoposide, camptothecin, CPT-11 (Pharmacia/UpJohn), doxorubicin, vincristine, davnorubicin, mitoxanthrone and colchicine), and ganciclovir and foscarnet. In preferred embodiments, fixed quantities of the bioavailability enhancing agent and the pharmaceutically active agent are formulated together in a combination oral dosage form. Such dosage forms can consist of tablets, capsules, caplets, gel caps, pills, liquids or lozenges. One such combination product includes from about 0.1 to about 20 mg/kg of one or more of cyclosporins A, D, C, F and G, dihydro CsA, dihydro CsC and acetyl CsA together with about 20 to about 1000 mg/m^2 (based on average patient body surface area), and preferably about 50-200 mg/m^2, of paclitaxel, docetaxel, other taxanes or paclitaxel or docetaxel derivatives such as paclitaxel 2'-MPM or docetaxel 2'-MPM.

In other preferred embodiments, the solvent contains a polyalkoxylated castor oil such as CREMOPHOR® EL in an amount of from about 3 mg/ml to about 10 mg/ml.

In the case of the pharmaceutically active agents that exhibit anti-neoplastic activity, the co-administration of enhancing agent enhances activity at sites highly protected by MDR *e.g.*, the testes and the brain. Thus, the present invention facilitates treatment of brain tumors such as glioblastoma multiforme.

In yet other preferred embodiments, the enhancing agent or combination of enhancing agents is co-administered with the target agent or a combination of target agents 10 minutes prior to, concurrent with, and up to two (2) hours after administration of the target agent(s). In this fashion, the maximum dose of cyclosporin enhancer *e.g.*, an amount of about 30mg/kg of patient body weight, may be administered.

The following examples illustrate various aspects of the invention and demonstrate the unexpected, very substantial increase in the oral absorption of paclitaxel achieved. These examples are not intended, however, to limit the invention in any way or to set forth specific enhancing or target agents, dosage ranges, testing procedures or other parameters which must be used exclusively to practice the invention.

EXAMPLE 1

Six (6) healthy Sprague Dawley rats, all weighing from 225-275 grams and approximately six to eight weeks old, received a single oral dose of paclitaxel at 9 mg/kg. Blood samples were collected from the tail vein of each rat at 0.5, 1, 2, 3, 4 and 6 hours after the paclitaxel dose. The individual samples were centrifuged and the serum was separated. For each time interval, the six samples were composited to produce a single representative sample. All samples were assayed for unchanged paclitaxel by LC/MS with a lower limit of quantitation of 50 pg/ml.

The results of the study are graphically illustrated in the lower curve of FIG. 1, which indicates that the bioavailability of the orally administered paclitaxel in serum was less than 1%.

EXAMPLE 2

Ten (10) healthy Sprague Dawley rats with the same characteristics as those used in the study described in Example 1 were treated with 5 mg/kg of oral cyclosporin A followed later with another 5 mg/kg dose of oral cyclosporin A and 9 mg/kg of oral paclitaxel.

Blood samples were collected from the tail vein of each rat at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 and 24 hours after paclitaxel administration. After appropriate treatment of the samples and the creation of one composite sample for the group, the plasma from each sample was assayed for unchanged paclitaxel.

The results of this study are graphically illustrated in the upper curve of FIG. 1. It may be observed that the plasma levels of paclitaxel in this group of animals was several times higher during the first six hours than in the rats of Example 1 who received paclitaxel alone, that levels at or above the "target" therapeutic levels were maintained for (8) eight hours after dosing and that significant plasma levels were maintained throughout the 24-hour period.

EXAMPLE 3

A 71-year old man with prostate cancer for three years agreed to receive an oral dose of paclitaxel and an enhancer in the form of cyclosporin A. His body surface area was 2.04 square meters and his weight was approximately 84 kilograms. After an overnight fast, he received two doses of cyclosporin A (Sandimmune 5 mg/kg) one hour apart. Just after the second dose, the patient drank a Cremophor/alcohol-based solution dose of paclitaxel containing 180 mg dissolved in 120 ml of 5% dextrose in water, i.e., about 2.0 mg/kg of body weight or about 90 mg/m^2 of body area. Standard premedications, as one would use for short-term infusion of taxanes, were not given. After drinking the solution, the patient remarked that the taste was unpleasant. He experienced some loose stools for a few hours. He also

reported some flushing several hours after dosing which might have been related to the temporary cessation of his anti-hypersensitive medication. His clinical course was otherwise unremarkable.

Plasma samples were obtained at frequent intervals following the administration of paclitaxel and were assayed by LC/MS/MS. The plasma level results over time are shown in FIG. 2. Peak was reached about 4 hours post dosing and levels above 0.07 micromolar were achieved from about one to five hours. Levels comparable to those found in breast cancer patients receiving 96-hour intravenous infusions of paclitaxel (0.05 micromolar), were present for about 10-12 hours (Seidman *et al.*, J. Clin. Oncol. *14*:1877, 1996).

EXAMPLE 4

A 75-year old man with prostate cancer for several years received an oral dose of paclitaxel and cyclosporin A. His body surface area was 1.82 square meters and his weight was approximately 72 kilograms. After an overnight fast, he received the same regimen of cyclosporin A (Sandimmune 5 mg/kg) and oral paclitaxel (180 mg) as the patient in Example 1, which equaled about 2.5 mg/kg or about 100 mg/m^2 of paclitaxel in this patient. Again, standard premedications, as one would use for short-term infusions of taxanes, were not given. After drinking the solution, the patient remarked that the taste was unpleasant. He experienced some loose stools for a few hours. He also had a modest decline in blood pressure after dosing which may have been related to a vaso-vagal reaction secondary to his fasting state and blood draws. As a precaution the patient received about 100 ml of saline intravenously. After eating lunch he felt much better and the remainder of his clinical course was otherwise remarkable.

Plasma samples were obtained at frequent intervals following the administration of paclitaxel and were assayed by LC/MS/MS. The plasma level results over time are shown in FIG. 3. The peak level was almost 0.3 micromolar and occurred at 4 hours post dosing. Levels above 0.07 micromolar were

achieved from about one to ten hours. Again, levels comparable to those found in breast cancer patients receiving 96-hour intravenous infusions of paclitaxel, were present for about 12-15 hours.

FIG. 4 represents a composite of the paclitaxel concentration levels determined over time in rats (upper curve from FIG. 1) and in humans (curves from FIGS. 2 and 3) following oral administration of paclitaxel and two doses of oral cyclosporin spaced one hour apart, in accordance with the present invention.

EXAMPLE 5

Fifty-three (53) human patients with incurable malignancies received oral paclitaxel in combination with CsA on one occasion and, intravenous (i.v.) paclitaxel at a dose of 175 mg/m^2 as a 3-hour infusion on another. The oral and i.v. formulation of paclitaxel consisted of 6mg/ml paclitaxel, dissolved in CREMOPHOR® EL and ethanol 1:1 w/v. Patients received one of 9 dose levels. (See FIG. 5.) Dose levels 1 and 2 were randomized for either oral and i.v. administration. At all higher levels (3-9), patients received oral paclitaxel during course 1 and i.v. paclitaxel during course 2.

Prior to oral paclitaxel administration, patients received oral doses of CsA. Patients received one of 10 dose levels (FIG. 5). At dose levels 2-3, patients received an oral solution of CsA 10 minutes before receiving oral paclitaxel. At subsequent doses, CsA was administered in capsules 30 minutes before paclitaxel administration. At dose level 4, CsA was administered 10 minutes before and 2 hours after oral paclitaxel administration.

To prevent hypersensitivity, patients were premedicated with dexamethasone 20 mg orally, 12 and 6 hours prior to i.v. and oral paclitaxel administration, clemastine 2 mg i.v. and cimetidine 300 mg i.v. 30 minutes before i.v. and oral paclitaxel administration. Three patients at dose level 8 and all patients at dose level 9 did not receive the above premedication prior to oral paclitaxel administration because

no CREMOPHOR® EL was detected in plasma of patients treated at the lower doses of paclitaxel. To prevent nausea and vomiting, patients at dose levels 8 and 9 were given granisertron (Kytril®)1mg orally 1 hour prior to receiving CsA.

Paclitaxel levels in urine and plasma were determined using a validated a high performance liquid chromatography (HPLC) assay. CsA levels were determined from whole blood samples using fluorescence polarization immunoassay. Ethanol levels were measured from plasma using a gas chromatagraph. CREMOPHOR® EL levels were determined using validated HPLC.

The area under the concentration-time curve (AUC) was estimated by the trapezoidal rule with extrapolation to infinity using the terminal rate constant K. The terminal half-life (t1/2) was calculated as 0.693/k. Other parameters assessed were maximal concentration (Cmax), the time to maximal concentration (Tmax) and time spent above threshold concentrations of 0.05μM and 0.1μM (T>0.05μM, T>0.1μM). Cmax and Tmax were determined graphically. T> 0.05μM and T> 0.1μM were determined using linear logarithmic interpolation. The percentage of the administration dose recovered (U_{exer}) was calculated as the amount excreted in the urine divided by the actual administration dose multiplied by 100%. Statistical analysis of the data was performed using the Student's t-test and the Pearson correlation coefficient. A p value less than 0.05 was regarded as statistically significant.

The principal types of hematological toxicity after oral administration of paclitaxel were leukocytopenia and granulocytopenia (FIG. 6). These toxicities were short lasting and often pre-existing. The non-hematological toxicities after oral paclitaxel administration, shown in Figs. 7A and 7B, were nausea, vomiting and arthralgia/myalgia, and were generally mild. Any severe toxicities were short-

lived and uncomplicated. Toxicities commonly associated with CsA were not observed.

Pharmacokinetic parameters of oral paclitaxel administration are defined in FIG. 8. Dose escalation of oral paclitaxel from 60mg/m^2 to 120mg/m^2 in combination with CsA 15mg/kg resulted in significant increase in both AUC and T>0.1μM of paclitaxel. Mean AUC values for the doses 60mg/m^2 and 120 mg/m^2 were 1.65+/- 0.93μM/h and 2.55 +/- 2.29μM/h, respectively and mean T>0.1 μM were 3.7+/- 2.3h and 7.9 +/- 8.0h, respectively. Further dose increase of oral paclitaxel did not result on average in an additional significant increase in AUC or T>0.1 μM of paclitaxel. Increasing the CsA dose or splitting the dose did not result in a further increase in the AUC and T> 0.1 μM of paclitaxel compared to the single dose of 15mg/kg. Large inter-patient variability was observed at all dosage levels.

Pharmacokinetic parameters of CsA are defined in FIG. 9. Dose increment and scheduling of CsA resulted in higher AUC values of CsA but Cmax values were not increased. Dose escalation of paclitaxel did not produce significant differences in pharmacokinetics of CsA. CREMOPHOR® EL levels in plasma after oral administration of paclitaxel were undetectable at all paclitaxel dose levels (< 0.01% v/v).

The i.v. paclitaxel pharmacokinetic data were in agreement with previously observed results.

In summary, CREMOPHOR® EL, which can induce hypersensitivity in patients, is not absorbed through the gut when administered orally as a solvent agent for paclitaxel. Additionally, CREMOPHOR® EL may interfere with the absorption of paclitaxel thereby limiting the bioavailability of this drug. No hypersensitivity was observed in patients who did not receive premedication prior to oral paclitaxel administration. Therefore, paclitaxel can be administered orally without the consequence of hypersensitivity. In addition, the maximum effect of CsA on the enhancement of the

exposure to paclitaxel was observed at a single dose of CsA of 15mg/kg.

As various possible embodiments might be made of the above invention and as various changes might be made in the embodiments set forth above, it is to be understood that all matters herein described are to be interpreted as illustrative and not in a limiting sense.

WE CLAIM:

1. A method of reducing the incidence or severity of hypersensitivity reactions associated with parenteral administration of a taxane, comprising orally administering to a patient a formulation comprising a taxane, wherein said formulation causes hypersensitivity reactions when administered parenterally.

2. The method of claim 1 wherein said taxane is selected from the group consisting of paclitaxel, docetaxel, taxane 2'MPM salts, and polymorphs and hydrates thereof.

3. The method of claim 1 wherein said taxane comprises a derivative, analog or prodrug of paclitaxel or docetaxel.

4. The method of claim 3 wherein said prodrug is paclitaxel-2'MPM or docetaxel-2'-MPM.

5. The method of claim 1 wherein said taxane is paclitaxel or docetaxel.

6. The method of claim 1 wherein said taxane is present in said formulation in an amount of from about 60 to about 250 mg/m^2.

7. A method of selectively enhancing the bioavailability of a pharmaceutically active agent, comprising: orally co-administering to a patient a bioavailability enhancing agent and a formulation including a pharmaceutically active agent and at least one solvent that achieves active blood levels when administered parenterally, wherein said pharmaceutically active agent achieves



therapeutic blood levels but said solvent does not achieve active blood levels.

8. The method of claim 7 wherein said solvent comprises a polyalkoxylated castor oil.

9. The method of claim 8 wherein said formulation further comprises ethanol.

10. The method of claim 7 wherein said bioavailability enhancing agent is selected from the group consisting of cyclosporins A through Z, dihydro cyclosporin A, dihydro cyclosporin C, acetyl cyclosporin A, PSC-833 and SDZ-NIM 811.

11. The method of claim 10 wherein said bioavailability enhancing agent is cyclosporin A.

12. The method of claim 7 wherein said bioavailability enhancing agent is orally administered prior to orally administering said taxane formulation.

13. The method of claim 7 wherein said bioavailability enhancing agent is orally administered after orally administering said taxane formulation.

14. The method of claim 7 wherein said bioavailability enhancing agent is orally administered substantially simultaneously with orally administering said taxane formulation.

15. The method of claim 7 wherein said bioavailability enhancing agent is orally administered at a time from about one hour before to about two hours after orally administering said taxane formulation.

16. The method of claim 7 wherein said pharmaceutically active agent is a taxane.

17. The method of claim 16 wherein said taxane is selected from the group consisting of paclitaxel, docetaxel, taxane 2'MPM salts, and polymorphs and hydrates thereof.

18. The method of claim 16 wherein said taxane comprises a derivative, analog or prodrug of paclitaxel or docetaxel.

19. The method of claim 18 wherein said prodrug is paclitaxel-2'MPM or docetaxel-2'-MPM.

20. The method of claim 16 wherein said taxane is paclitaxel or docetaxel.

21. The method of claim 16 wherein said taxane is present in said formulation in an amount of from about 60 to about 250 mg/m^2.

22. A composition comprising a taxane and a polyalkoxylated castor oil, wherein said composition is in the form of an oral dosage unit.