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Tocosol® Paclitaxel

Anticancer Formulation

S-8184

Cremophor-free, vitamin E-based paclitaxel emulsion

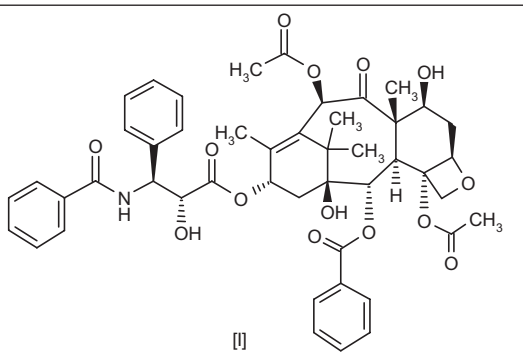
EN: 299083

Abstract

Paclitaxel is an important anticancer agent with a wide range of activity against solid tumors. However, the available paclitaxel-based anticancer formulations, such as Taxol®, are associated with numerous drawbacks, including expensive and time-consuming drug preparation, long infusion periods and adverse side effects. Tocosol® Paclitaxel (S-8184), a Cremophor-free, vitamin E-based paclitaxel emulsion, has been designed to overcome the limitations associated with Taxol®- and generic paclitaxel-based chemotherapy. Tocosol® Paclitaxel is a ready-to-use formulation, and it allows a dose of paclitaxel to be administered to patients in 15 min instead of the 3 h required with Taxol®. Preclinical and clinical results to date have shown that Tocosol® Paclitaxel has less toxicity and greater anticancer efficacy than Taxol®. Tocosol® Paclitaxel is currently in phase III trials for the treatment of metastatic breast cancer.

Background

Paclitaxel [I] is an important chemotherapeutic agent with a wide spectrum of activity against solid tumors, including breast, ovarian, colon and non-small cell lung cancer (NSCLC). Paclitaxel has proven to be one of the most broadly effective, and to date the most commercially successful, anticancer agent. The drug exerts its anticancer activity by binding to tubulin and stabilizing microtubules, thus blocking cell mitosis. Like most natural products, however, paclitaxel has limited aqueous solubility (1, 2).



[I]

In conventional parenteral formulations, nonaqueous solvents such as ethanol and solubilizers such as polyoxyethylated surfactants (Cremophor EL) are often used to enhance the solubility of water-insoluble drugs. Taxol® (Bristol-Myers Squibb Oncology), the first and highly successful paclitaxel-based anticancer drug, is formulated in a 1:1 (v/v) mixture of Cremophor EL and ethanol. Cremophor EL, however, has serious side effects, including bronchospasm, hypotension and other manifestations of hypersensitivity. Dilution of the ethanol:Cremophor EL solution, a long infusion period, as well as corresponding premedication, are therefore required to reduce the adverse effects. Moreover, the ethanol:Cremophor-based formulation is associated with a number of issues, including drug stability, requirement for filtering, nonplasticized containers and administration sets. To overcome the limitations associated with Taxol®- and generic paclitaxel-based chemotherapy, Sonus designed Tocosol® Paclitaxel using vitamin E and vitamin E derivatives to solublize, stabilize and formulate paclitaxel with the goal of enhancing its delivery, safety and efficacy (1, 2).

Vitamin E is a member of the tocol family, which are known to be excellent solvents for water-insoluble drugs. Tocols are compatible with other co-solvents and surfactants, and tocol emulsions have been widely used in drug delivery. Compared to aqueous solvents, emulsions generally have many advantages, including lower toxicity, slower release of active drugs, better stability and duration. Emulsions of tocols have the added advantage that the emulsions themselves, such as vitamin E and vitamin E derivatives, may contribute therapeutic value in certain conditions. Tocosol® Paclitaxel is a Cremophor-free, vitamin E-based paclitaxel emulsion designed to reduce toxicity, shorten the infusion period and hopefully increase anticancer efficacy (1-3). Tocosol® Paclitaxel is the only tocol emulsion currently in clinical development and is undergoing phase III evaluation in women with metastatic breast cancer (4, 5).

Preclinical Pharmacology

The anticancer efficacy of Tocosol® Paclitaxel was compared to Taxol® in mice with a variety of tumors,

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including B16 melanoma and human colon cancer HCT-15. As a fast-growing solid murine tumor, B16 melanoma is often used in early screening of a variety of anticancer agents. Compared to the tumor-bearing mice treated with Taxol® at equivalent doses, mice administered Tocosol® Paclitaxel showed significant tumor growth inhibition. At a dose of 20 mg/kg, the administration of Taxol® resulted in 50% mortality and showed minimal antitumor efficacy, whereas Tocosol® Paclitaxel showed no mortality and much improved antitumor efficacy, as well as 2 times better tolerance. HCT-15 is an aggressive human colon tumor cell line that shows little response to Taxol®. HCT-15 cells exhibit a high level of P-glycoprotein activity, which removes many drugs, including paclitaxel, from the cell. Mice implanted with HCT-15 tumors were treated with Tocosol® Paclitaxel or Taxol® seperately at the same dose (15 mg/kg), with Tocosol® Paclitaxel showing improved efficacy (1).

Pharmacokinetics and Metabolism

In vitro studies showed that the release of paclitaxel from emulsions (< 5% being released over 24 h) is slower than from Taxol® (12% released over 24 h). The slow drug release from emulsions suggests that emulsion drug droplets may serve as long-circulating drug reserviors (2).

To understand why Tocosol® Paclitaxel shows better antitumor activity than Taxol®, the tissue distribution of paclitaxel released from Tocosol® Paclitaxel and Taxol® was compared. It was observed that the total paclitaxel concentration in the blood was very similar following administration of the two formulations. However, the paclitaxel concentration in the tumor following the administration of Tocosol® Paclitaxel was significantly higher, particularly at 4 h postdose. The resulting maximum concentration of paclitaxel in the tumor was 1.5 times higher following Tocosol® Paclitaxel, and the extent of tumor exposure, as measured by the area under the curve (AUC), was approximately 2.2 times higher (1, 3).

Pharmacokinetic comparision of Tocosol® Paclitaxel and Taxol® was performed in 36 patients with solid tumors without other treatment options. Patients were given an equal dose (175 mg/m^2) of either Tocosol® Paclitaxel or Taxol® over 21 days. Compared to Taxol® administered over 3 h, Tocosol® Paclitaxel given over 15 min showed an average 67% and 108% higher free and total paclitaxel exposure, respectively. The difference in drug exposure may reflect the difference in the dissociation rate of paclitaxel from the two different formulations. Tocosol® Paclitaxel and Taxol® showed a similar paclitaxel terminal elimination half-life ($t_{1/2}$) (6).

Safety

Preclinical studies showed that the maximum tolerated dose (MTD) of Tocosol® Paclitaxel is 3 times higher than Taxol®, indicating that Tocosol® Paclitaxel is less toxic (3).

In a dose-escalating phase I study performed in patients with advanced solid malignancies, Tocosol® Paclitaxel was given at doses of 25-225 mg/m^2 as a 15-min i.v. push. Neutropenia and febrile neutropenia were found to be the main dose-limiting toxicities. No severe neuropathy was noted. The study suggested that Tocosol® Paclitaxel can be given safely via i.v. push, and no patient required steroid premedication, which is necessary with Taxol® to suppress allergic reactions (3).

In four separate phase II studies performed in patients with ovarian, colorectal or bladder cancer or NSCLC, Tocosol® Paclitaxel was well tolerated at a dose of 120 mg/m^2 given weekly. Grade 3 or 4 neutropenia was observed in only about one-third of the patients, with no sepsis or septic deaths. About one-third of the patients suffered neuropathy, but no severe (grade 4) neuropathy was observed. Most of the patients received full doses on time, or resumed the full dose rapidly if dose reduction was required. Infusion reactions were uncommon and generally mild, and did not prevent delivery of the intended dose of the drug (7).

The most frequent toxicity reported in a phase IIb study in patients with metastatic breast cancer was neutropenia (grade 3 or 4); 60% of the patients required a dose reduction by week 4, but most of them returned to a full dose in a week. Grade 3 neuropathy was reported in about 11% of the patients, but no grade 4 neuropathy was observed. Mild arthralgias and myalgias were reported in 34% of the patients and 51% of the patients had adverse events related to infusion. Only 1 grade 4 event (sacral pain) was reported and resulted in withdrawal from the study after 3 episodes. In all other patients, infusion reactions were easily managed and did not result in discontinuation of the therapy (8).

Clinical Studies

To evaluate the efficacy of Tocosol® Paclitaxel in specific tumor types and to build on the encouraging tumor responses observed in the phase I study (3), four parallel, open-label phase II studies were performed in patients with NSCLC, ovarian, bladder or colorectal cancer (9).

In one of the phase IIa studies, 43 patients with advanced (stage III or IV) NSCLC who were previously treated with platinum-based therapy received Tocosol® Paclitaxel (80, 100 and 120 mg/m^2 i.v. over 15 min) once weekly for a median of 15 weeks. The objective response rate was about 21%, with 7% of the patients achieving a complete response and 14% a partial response. Approximately 43% of patients had stable disease. Over half of the patients discontinued treatment for various reasons, including adverse events, investigator's decision, progressive disease or unspecific reasons, but < 5% of patients discontinued the trial due to adverse events (10).

As part of the phase IIa program, a multicenter study of Tocosol® Paclitaxel was conducted in 52 female patients with stage III/IV platinum-resistant ovarian cancer. The patients were given the drug at doses of 80, 100 or 120 mg/m^2 i.v. over 15 min weekly for a median of 9 weeks. Sixteen patients (31%) achieved a complete or

partial response and 18 patients had stable disease. Tocosol® Paclitaxel treatment was discontinued due to adverse events in 5 patients, investigator's decision in 6, unspecified reasons in 13 and progressive disease in 23 (11).

Another multicenter phase IIa study of second-line Tocosol® Paclitaxel was performed in 27 taxane-naïve patients with metastatic or locally advanced, unresectable or recurrent urothelial transitional cell cancer (TCC) who progressed after cisplatin-based therapy. Tocosol® Paclitaxel (80, 100 and 120 mg/m^2 i.v. over 15 min) was given once weekly for a median of 16 weeks. Nine patients (33%) had a complete or partial response and 11 patients (40%) showed stable disease. Tocosol® Paclitaxel was discontinued in 3 patients who were treated surgically, in 8 for unspecified reasons, in 7 due to adverse events and in 2 due to investigator's decision. Two patients were lost to follow-up and 5 had progressive disease (12).

To evaluate the safety and efficacy of Tocosol® Paclitaxel as an initial treatment for patients with metastatic cancer, 47 patients with previously untreated metastatic breast cancer were enrolled in an ongoing phase IIb study. The mean dose delivered was 95 mg/m^2 weekly. Twenty-seven patients remained on therapy after an average of 17 weeks and 20 patients discontinued for various reasons. Investigators reported an objective response rate of 48%. Based on the results of this study, the recommended dose for phase III trials was 100 mg/m^2 weekly (8).

Sonus initiated a pivotal phase III trial of Tocosol® Paclitaxel in September 2005. The trial will enroll approximately 800 women with metastatic breast cancer, who will receive either Tocosol® Paclitaxel or Taxol® on a weekly dosing schedule. The phase III trial will be conducted at approximately 150 clinical study sites in North America, Western and Eastern Europe, South Africa and Israel. The 2-arm, randomized study is being conducted under a special protocol assessment (SPA) that Sonus completed with the FDA in June 2005. The primary endpoint is objective response rate, and an NDA will be submitted based on analyses of data for that endpoint. Secondary endpoints of progression-free survival and overall survival are included in the trial design, and patient follow-up for those endpoints will continue following NDA submission (4, 5, 13, 14).

Sources

Sonus Pharmaceuticals, Inc. (US); licensed worldwide to Schering AG (DE).

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