Introduction

Paclitaxel (Taxol) is a natural product originally extracted from the bark of the Pacific yew tree, Taxus brevifolia, which is now semisynthetically produced from reproductive material of the European yew tree, Taxus baccata. It is an antineoplastic drug that acts at the cellular level as a promoter of microtubule assembly from tubulin dimers, stabilizing microtubules by preventing depolymerization. After intravenous administration, paclitaxel is metabolized in the liver and high concentrations are excreted in the bile. Its dose-limiting toxicities include myelosuppression (mostly neutropenia of a short duration), peripheral neuropathy, hypersensitivity reactions, and mucositis. Paclitaxel was initially investigated in phase I/II trials as a treatment for ovarian cancers that were refractory to platinum therapy and for advanced breast cancer. In metastatic breast cancer, response rates of up to 56% have been reported[1] following paclitaxel monotherapy, with results mainly dependent on the pretreatment history of patients. In multicenter trials, response rates were lower, but relatively good survival results have been achieved.[2] Clinical trials in nongynecologic malignancies are ongoing. So far, promising results have been observed in small-cell and non–small-cell lung cancer,[3] bladder cancer,[4] esophageal cancer,[5] head and neck cancer,[6] and others.[7]

Initially, paclitaxel was administered as a 24-hour infusion to avoid the hypersensitivity reactions observed in an early phase I trial of paclitaxel in a 3-hour infusion.[8] Since premedication with corticosteroids (most often, dexamethasone), diphenhydramine, and cimetidine was introduced into clinical practice, however, the risk of hypersensitivity reactions has been largely eliminated.[9] Recently, published reports have shown that a short course of intravenous prophylaxis is sufficient for the prevention of hypersensitivity reactions,[10] thereby enabling reinstitution of shorter paclitaxel infusions. Thus, a 1-hour infusion of paclitaxel, which permits the convenience of outpatient treatment, was investigated in phase I trials. Hainsworth et al and Mross et al showed that paclitaxel administered as a 1-hour infusion is safe and produces substantial activity in a variety of tumors.[11,12] These studies reinforced the observation that the myelotoxicity of paclitaxel is schedule-dependent, with longer infusions producing greater hematologic adverse effects.

Several clinical trials have also examined weekly administration of paclitaxel.[1,13-17] An overview is provided in Table 1. In general, these trials showed that weekly administration of paclitaxel yields a high dose intensity with limited hematologic toxicities. Long-term use of weekly paclitaxel with doses of more than 100 mg/m²/week may result in treatment-limiting neurotoxicity. However, objective responses in phase II trials in heavily pretreated patients have been rather high so far. 5-fluorouracil (5-FU) is a fluorinated pyrimidine that works as an antimetabolite. The compound was developed in 1957 based on the observation that tumor cells use the base uracil for deoxyribonucleic acid (DNA) synthesis more efficiently than normal cells of the intestinal mucosa. The drug is then rapidly metabolized by the human liver, resulting in a short half-life of 10 to 20 minutes. In human tumors, 5-FU is metabolized to 5-fluorouridine-5′-monophosphate (FUMP) and subsequently converted to the active nucleotides, 5-fluorouridine 5′-triphosphate (FUTP) and 5-fluoro-2′-deoxyuridine 5′-monophosphate (FdUMP). The primary mechanism of 5-FU cytotoxicity in experimental tumors appears to be FdUMP inhibition of thymidylate synthase, and consequently, inhibition of DNA synthesis.[18]
The cytotoxic effects of 5-FU can be markedly enhanced if sufficient amounts of reduced folate cofactor are present.[19,20] The biochemical modulation of 5-FU by calcium folinate has been extensively studied in patients with metastatic colon carcinoma. Clinical trials examining 5-FU plus calcium folinate have demonstrated increased response rates, prolonged time to disease progression, and prolonged overall survival as compared to single-agent 5-FU.[21]

UFT is composed of uracil and tegafur (1-[2′-tetrahydrofuryl]-5-fluorouracil) in a molar ratio of 4:1. Tegafur is converted to 5-FU in vivo. Tanimura et al reported that the coadministration of uracil enhanced the concentration of 5-FU in tumors and the resulting antitumor activity of UFT.[22,23] Following oral administration of UFT, uracil and tegafur are rapidly and completely absorbed from the gut into the systemic circulation. Tegafur is subsequently metabolized to 5-FU by one of two different pathways and enzyme systems, thereby behaving as a prodrug of 5-FU.[24]

Pazdur has shown that UFT administered at a daily dose of 370 mg/m²/day for 28 days without calcium folinate generates a higher peak plasma level of 5-FU than that achieved with continuous infusion 5-FU at 250 mg/m²/day for 5 days.[25] Several phase I studies of UFT plus oral calcium folinate have been performed.[26-28] The maximum tolerated dose of UFT was 350 to 400 mg/m²/day × 28 days, in combination with calcium folinate 150 mg/day × 28 days. One cycle consisted of 35 days. The major dose-limiting adverse event was diarrhea. Nausea, vomiting, abdominal cramping, epigastralgia, and stomatitis/mucositis were also observed. These events increased in severity with increasing doses of UFT plus oral calcium folinate. Other minor events in these phase I studies included mild fatigue, transient hyperbilirubinemia, anorexia, and granulocytopenia. The efficacy of oral UFT in combination with oral calcium folinate in the home setting has been demonstrated in phase II studies that evaluated a total of 140 patients with metastatic colorectal carcinoma.[29,30] Responses were reported in a variety of metastatic sites, including the liver, lung, and bone, yielding response rates from 25% to 42%. UFT also exhibited clinical efficacy in a number of other tumors, including carcinomas of the stomach,[31] head and neck,[32] non-small-cell lung cancer,[33] and breast cancer.[34] This corresponds to the clinical activity of 5-FU.

Phase I Study of UFT/Calcium Folate Plus Weekly Paclitaxel

Background
Because many cases of cancer are incurable, palliation of symptoms and improved quality of life are critical aspects of therapy. A high level of efficacy, especially in second- and third-line treatments, few side effects, and patient convenience are equally important. This open-label phase I study was designed to evaluate the combination of UFT plus oral calcium folinate plus a 1-hour infusion of paclitaxel for the treatment of patients with solid tumors, for whom no other established therapy exists.

UFT plus calcium folinate is an oral agent with activity comparable to intravenously administered 5-FU plus calcium folinate. Paclitaxel, administered on a weekly schedule, leads to high dose intensity and high response rates with limited hematologic toxicities. Thus, this outpatient regimen offers the advantages of oral delivery of 5-FU and a weekly paclitaxel infusion, which requires minimal monitoring. Myelosuppression is infrequent with UFT plus calcium folinate therapy and its side effects should compare favorably with commonly used regimens.

It is the primary objective of this study to determine the dose-limiting toxicity(ies), maximum-tolerated dose, and recommended phase II dose of weekly paclitaxel administered in combination with a stable dose of UFT plus calcium folinate in adult patients with solid tumors. The secondary objectives are to further evaluate the safety of this combination and to obtain preliminary efficacy data. In the event that a positive risk-benefit ratio is observed, the combination of UFT plus calcium folinate and weekly infusional paclitaxel could be useful in a number of tumor types.

The study has been approved by the Ethics Committee of Tübingen University. It will be conducted as a multicenter trial with the German Phase I/II study group of the Working Party for Medical Oncology (Deutsche Phase I Studiengruppe der AG Internistische Onkologie).

Patients
A number of criteria must be met for patients to be eligible for admission to the study. Patients must have a histologically confirmed diagnosis of a solid tumor for which no other established therapy exists, such as extensive-stage small-cell or non-small-cell lung cancer, inoperable head and neck or bladder cancer, or previously treated ovarian or breast cancer. Patients may or may not have received prior chemotherapy, hormonal therapy, or localized radiation therapy. Patients must be between 18 and 70 years, they must have an Eastern Cooperative Oncology Group performance score of 0-2, and must be able to understand and consent to the study.
status of 0 to 2, and a life expectancy of ≥ 12 weeks. Adequate hematologic, renal, and hepatic functions are also required for investigational protocols. Patients will be excluded if they have a significant history of cardiac disease (ie, uncontrolled high blood pressure, unstable angina, congestive heart failure, myocardial infarction within the previous year, or cardiac ventricular arrhythmias requiring medication); severe, active infections; or serious underlying medical conditions. Brain metastases or evidence of grade ≥ 2 peripheral neuropathy (National Cancer Institute [NCI] Common Toxicity Criteria) are also exclusion criteria.

**Treatment Regimen**

UFT will be administered at a fixed dose of 300 mg/m²/day plus calcium folinate 90 mg/day for 28 days (days 1–28) followed by 1 week without treatment. This 35-day period defines the length of a treatment cycle. Both UFT and calcium folinate will be orally administered in three daily doses, with 8-hour intervals between doses.

Following adequate premedication, a single 1-hour intravenous infusion of paclitaxel will be administered in 1-week intervals (days 1, 8, 15, 22), followed by a 1-week period without treatment; ie, re-treatment will start at day 36. The starting dose of paclitaxel will be 50 mg/m², escalated stepwise in subsequent cohorts of patients to 60 mg/m², 70 mg/m², 80 mg/m², 90 mg/m², and then 100 mg/m² ([Figure 1](#)). Higher doses will not be administered in order to avoid peripheral neurotoxicity.

A minimum of three patients will be treated at each dose level, and there will be no dose escalation for any given patient. All patients to be treated at a given dose level will have had to complete course 1, with a full evaluation of toxicity corresponding to dose-limiting toxicity and maximum tolerated dose criteria, before escalation to the next dose level in a new cohort of patients. These criteria may entail treatment of additional patients at the dose level in order to more fully define the toxicity profile before dose escalation.

If one of the first three patients at a given dose level experiences a dose-limiting toxicity, three more patients will be treated at this dose level. If none of the three patients or two or less of six patients experience a dose-limiting toxicity during their first course of treatment, the next dose level will be opened. If serious toxicities occur during later courses, dose escalation may have to be reconsidered. If three or more of six patients experience a dose-limiting toxicity at a dose level, that level will be regarded as the maximum tolerated dose.

After the maximum tolerated dose has been reached, 10 additional patients will be treated at one dose level below the maximum tolerated dose to evaluate the cumulative toxicity and to establish the recommended dose for phase II. If the maximum tolerated dose has not been reached during dose escalation, 10 additional patients will be treated at the highest dose level (100 mg/m²) ([Table 2](#)). Patients will be treated for a maximum of four cycles or until progression of disease or unacceptable toxicity occurs. Patients will not be re-treated unless they have recovered completely from toxicity (hematologic and/or nonhematologic). Patients who require more than 2 weeks of treatment delay will be removed from the study.

**Evaluation of Response/Toxicity**

All patients will be evaluable for toxicity from the time of their first chemotherapy dose. Toxicity will be evaluated using the NCI Common Toxicity Criteria scale. Patients will be evaluable for response if they have received at least one full course of therapy. The World Health Organization criteria will be used to assess tumor response. Time to progression will be calculated for all patients from the first day of treatment until the first evidence of disease progression or death. Three to six patients will be tested at each dose level. It is estimated that 30 to 40 patients must be enrolled to determine the maximum tolerated dose and the recommended phase II dose ([Table 3](#)). Descriptive statistics will be employed in the analysis of all safety and laboratory observations and efficacy data (response rate and time to progression).

**Discussion**

The combination of paclitaxel and 5-FU constitutes a promising regimen that has been investigated mainly in breast cancer patients. Anthracycline and alkylating agent-based regimens are routinely used as first-line chemotherapy in metastatic breast cancer; however, disease progression often occurs during or after this treatment, thereby requiring additional therapies.

In recent studies, response rates of 54% to 69% have been reported for the combination of calcium folinate/5-FU/paclitaxel as salvage chemotherapy after prior exposure to mostly anthracycline-containing regimens.[35,36] A 55% overall response rate, with a median duration of 8
months, was achieved in one of these studies involving 20 patients with anthracycline-refractory disease. In this study, calcium folinate 500 mg/m² was administered as a 2-hour infusion prior to administration of 5-FU and paclitaxel. 5-FU was administered at a dose of 2.0 g/m² over 24 hours and paclitaxel 175 mg/m² was infused over 3 hours. All drugs were administered on day 1, and calcium folinate and 5-FU were repeated weekly on days 8 and 15. Treatment was repeated every 3 weeks. A phase II trial of first-line treatment of metastatic breast cancer with infusional 5-FU, folic acid, paclitaxel, and cisplatin (Platinol)[37] achieved an overall response rate of 82% with only moderate side effects. The high response rates observed in these studies support the use of prolonged fluoropyrimidine exposure.

The combination of paclitaxel and 5-FU has also been successfully employed in the treatment of patients with gastrointestinal cancers. Partial remissions were observed in 32% of patients in a phase II trial using a 24-hour continuous infusion of high-dose 5-FU administered weekly in combination with paclitaxel every second week as a short infusion in patients with gastric cancer.[38] The further development of this regimen includes alternating the weekly doses of paclitaxel and cisplatin combined with continuous 24-hour infusions of 5-FU. Activity has also been reported with paclitaxel/5-FU combinations in patients with esophageal cancer. This regimen—possibly with the addition of cisplatin—may also be used for neoadjuvant treatment in this disease.[39]

A phase I trial of UFT plus calcium folinate with paclitaxel as second-line treatment of metastatic breast cancer is currently ongoing. In this study, a single infusion of paclitaxel at a fixed dose of 175 mg/m² is administered over 3 hours intravenously on day 1. Oral UFT plus calcium folinate is then administered for 14 days followed by a 1-week period without treatment. This therapy is repeated every 21 days. UFT is escalated in 100-mg increments from a total starting dose of 300 mg/day; calcium folinate dose is fixed at 30 mg three times a day.

**Conclusion**

The study described herein will take the use of protracted 5-FU (administered orally as UFT plus calcium folinate) in combination with paclitaxel one step further by applying paclitaxel in a dose-dense, moderately toxic weekly schedule. It is hoped that an active palliative regimen for the outpatient treatment of a variety of patients and cancers will result.

**References:**


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