UFT/Leucovorin Plus Weekly Paclitaxel in the Treatment of Solid Tumors

Introduction

Paclitaxel (Taxol) is a natural anti-cancer drug originally extracted from the bark of the Pacific yew tree *Taxus brevifolia*, and now semisynthetically produced from reproductive material of the European yew tree *Taxus baccata*. It acts at the cellular level as a promoter of microtubule assembly from tubulin dimers and stabilizes microtubules by preventing depolymerization.

Paclitaxel was initially investigated in ovarian cancer patients refractory to cisplatin (Platinol) or carboplatin (Paraplatin) and in patients with advanced breast cancer.[1,2] The drug is now approved for the treatment of ovarian, breast, and non–small-cell lung cancer. Additionally, promising results have been observed in small-cell lung cancer,[3] bladder,[4] esophageal,[5] head and neck,[6] and gastric cancers.[7]

When paclitaxel is given as a 24-hour infusion, the dose-limiting toxicities have been identified as myelosuppression (mostly neutropenia of short duration), peripheral neuropathy, hypersensitivity reactions, and mucositis. Paclitaxel was administered as a 24-hour infusion because hypersensitivity reactions constituted a treatment-limiting toxicity in an early phase I trial.[8] The clinical use of premedication with corticosteroids (most often dexamethasone), diphenhydramine, and cimetidine has reduced the frequency of these hypersensitivity reactions. A short course of intravenous prophylaxis has been shown to be sufficient for the prevention of hypersensitivity reactions. A 1-hour paclitaxel infusion was introduced mainly for the convenience of outpatient treatment. Hainsworth et al and Mross et al showed that paclitaxel given as a 1-hour infusion is safe and has substantial activity against a variety of tumors.[10,11] These studies also confirmed that myelotoxicity with paclitaxel was schedule-dependent.

Several clinical trials have examined weekly administration of paclitaxel. These trials indicate that a high dose intensity is reached with very limited hematologic toxicities. The long-term use of weekly paclitaxel with doses > 80 mg/m²/wk may result in treatment-limiting neurotoxicity appearing 8 to 12 weeks into therapy. However, objective responses in heavily pretreated patients with breast and ovarian cancer have been reported.[12-15]

Fluorouracil (5-FU), an antineoplastic antimetabolite, is a fluorinated pyrimidine. This drug is very rapidly metabolized by the human liver, resulting in a very short half-life of 10 to 20 minutes. In human tumors, 5-FU is metabolized to fluorouridine monophosphate and is subsequently converted to the active nucleotide forms fluorouridine triphosphate and fluorodeoxyuridine monophosphate. The primary mechanism of cytotoxicity in experimental tumors appears to be fluorodeoxyuridine monophosphate inhibition of thymidylate synthase and, consequently, inhibition of DNA synthesis.[16]

The cytotoxic effects of 5-FU can be enhanced if sufficient amounts of reduced folate cofactor are present.[17,18] The biochemical modulation of 5-FU by leucovorin has been extensively studied in patients with metastatic colon carcinoma. Clinical trials utilizing 5-FU with leucovorin have demonstrated increased response rates, prolonged time to disease progression, and possibly prolonged overall survival as compared to single-agent 5-FU.[19] UFT is composed of tegafur (1-[2´-tetrahydrofuryl]-5-fluorouracil) and uracil in a molar ratio of 1:4. Tegafur is converted to 5-FU in vivo. Tanimura reported that the coadministration of uracil enhanced the concentration of 5-FU in tumors and the resulting antitumor activity of UFT.[20,21] 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 to 5-FU.[22] Pazdur et al has shown that UFT given at a daily dose of 370 mg/m²/d for 28 days without leucovorin generates a higher peak plasma level of 5-FU than can be achieved with continuous infusion of 5-FU given at a dose of 250 mg/m²/d for 5 days.[23] This suggests that the same principle of biomodulation with leucovorin can be applied to UFT. In phase I studies of UFT and oral leucovorin, the dose-limiting adverse event was diarrhea.[24-26] Nausea, vomiting, abdominal cramping, epigastralgia, and stomatitis/mucositis were also observed. These events increased in severity with increasing doses of UFT and oral leucovorin. Other minor events included mild fatigue, transient hyperbilirubinemia, anorexia, and granulocytopenia.

The efficacy of oral UFT in combination with oral leucovorin when administered on an outpatient basis has been demonstrated in phase II studies of patients with metastatic colorectal carcinoma.[27] Responses were reported in a variety of metastatic sites including liver, lungs, and bone, yielding rates from 25% to 42%. Recently, two randomized phase III studies demonstrated a comparable efficacy but less toxicity with UFT plus leucovorin compared with a 5-day bolus 5-FU plus leucovorin schedule in patients with metastatic colorectal cancer.[28,29] UFT has shown clinical efficacy corresponding to the clinical activity of 5-FU in a number of other tumors, including carcinomas of the stomach,[30] head and neck,[31] non-small-cell lung cancer,[32] and breast cancer.[33]

This article describes a phase I study investigating the combination of oral UFT plus leucovorin in combination with a 1-hour infusion of paclitaxel in patients with solid tumors for whom no other established therapy exists.[34] Compared with other cancer treatment regimens, this combination has the advantages of an oral regimen in combination with a weekly infusion of paclitaxel, which requires minimal monitoring. Previous studies suggest that myelosuppression following UFT plus leucovorin is observed infrequently and that the side effects of treatment should compare favorably with commonly used regimens.[26-28]

The primary objective of this study is to determine the dose-limiting toxicity, the maximum tolerated dose, and the recommended phase II dose of weekly paclitaxel given in combination with a fixed dose of UFT and leucovorin in adult patients with solid tumors.

**Treatment and Patients**

**Treatment**

This study is an open-label, phase I trial with UFT given at a dose of 300 mg/m² in combination with 90 mg absolute leucovorin for 28 days (days 1 to 28) followed by a 1-week period without treatment. This 35-day period defines the length of a treatment cycle. UFT and leucovorin are given orally, with the total daily dose divided into three doses with 8-hour intervals.

Following adequate premedication, a single 1-hour infusion of paclitaxel is administered intravenously in 1-week intervals (days 1, 8, 15, and 22) followed by a 1-week period without treatment. The starting dose of paclitaxel was 50 mg/m². Paclitaxel is stepwise escalated in 10 mg/m² increments up to 100 mg/m² (Table 1). The dose of UFT plus leucovorin will not be escalated during this trial.

A minimum of three patients are treated at a given dose level, and there is no intrapatient dose escalation. All patients to be treated at a given dose level must complete course 1, with a full evaluation of toxicity at that dose level, before escalation to the next dose level in a subsequent cohort of patients.

If one of the first three patients at a given dose level experiences a dose-limiting toxicity, three more patients are treated at this dose level. If a total of three or more of six patients experience a dose-limiting toxicity at a given dose level, that dose level will be regarded as the maximum tolerated dose. Definitions of dose-limiting toxicity are shown in Table 2.

After the maximum tolerated dose has been reached, 10 additional patients will be treated at one dose level below the maximum tolerated dose for evaluation of the cumulative toxicity and to determine the recommended dose for phase II. Patients are treated for a maximum of four cycles, or until progression of disease or unacceptable toxicity occurs. Toxicity will be evaluated using the Common Toxicity Criteria scale. Patients are evaluable for response if they have received at least one full course of therapy. World Health Organization criteria will be used for assessment of tumor response. The study has been approved by the Ethics Committee of Tuebingen University and is conducted as a multicenter trial within the German phase
I/II study group for the Working Party For Medical Oncology.

**Patients**

For study eligibility, 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. Requirements include age > 18 years and < 70 years, Eastern Cooperative Oncology Group performance status 0 to 2, and life expectancy ≥ 12 weeks. Adequate hematologic, renal, and hepatic functions are required.

Patients with a significant history of cardiac disease, ie, uncontrolled high blood pressure, unstable angina pectoris, congestive heart failure, myocardial infarction within the previous year, or cardiac ventricular arrhythmia requiring medication, or patients with severe active infections or other serious underlying medical conditions are excluded.

Currently, 26 patients with a median age of 57 years have been entered into protocol. Tumor types included are non-small-cell lung cancer (18 patients), small-cell lung cancer (3 patients), bladder cancer (3 patients), and ovarian and head and neck cancer (1 patient each) (Table 3). Currently, six patients have been entered at dose level 4 with paclitaxel 80 mg/m² weekly. Fourteen patients are fully evaluable at this time, with a median 2.2 cycles applied per patient (range: 1–5 cycles). The dose-limiting toxicities observed have been diarrhea in four patients and fatigue syndrome in two patients.

The preliminary assessment of toxicities is summarized in Table 4. There was a surprisingly low incidence of peripheral neuropathy, with five patients developing grade 1/2 toxicity. The hematologic side effects were also mild and did not exceed grade 2. Interestingly, seven patients experienced fatigue syndrome rated grade 1 or 2 and two patients experienced dose-limiting grade 3 fatigue syndrome. One of these patients, with non-small-cell lung cancer, was not able to carry on her daily household activities during treatment, and fully recovered from fatigue within 4 weeks after discontinuation of protocol therapy.

Preliminary responses have been observed in 14 evaluable patients, with three patients achieving a partial remission and four patients with disease stabilization. Recruitment into the protocol is continuing.

**Discussion**

The combination of paclitaxel and 5-FU constitutes a promising regimen that has been previously investigated in breast cancer patients after treatment with anthracycline- and alkylating-agent-based regimens. Response rates of 54% to 69% have been reported for the combination of leucovorin/5-FU/paclitaxel as salvage chemotherapy after prior exposure to mostly anthracycline-containing regimens.[35,36] In one study of 20 patients with anthracycline-refractory disease, a 55% overall response rate and a median response duration of 8 months were achieved. In this study, leucovorin 500 mg/m² was administered as an infusion given over 2 hours prior to 5-FU and paclitaxel. 5-FU was given at a dose of 2 g/m² over 24 hours and paclitaxel 175 mg/m² was infused over 3 hours.

In a phase II trial[37] of intravenous 5-FU, folinic acid, paclitaxel, and cisplatin as a first-line treatment of metastatic breast cancer, an overall response rate of 82% with only moderate side effects was achieved. The high response rates observed in these studies support the use of prolonged fluoropyrimidine in combination with paclitaxel.

The combination of paclitaxel and 5-FU has also been successfully employed in the treatment of patients with gastrointestinal cancers. In a phase II trial of 24-hour, continuous-infusion, high-dose 5-FU given weekly in combination with short-infusion paclitaxel every second week in patients with gastric cancer, partial remissions were observed in 32% of patients.[7] Further development of this regimen includes alternating weekly doses of paclitaxel and cisplatin combined with continuous 24-hour infusions of 5-FU. Activity has also been reported for paclitaxel/5-FU combinations in patients with esophageal cancer, and this regimen[possibly with the addition of cisplatin][may also be used for neoadjuvant treatment of this disease.[38]

A phase I trial of UFT and paclitaxel as a second-line treatment of metastatic breast cancer has used a single infusion of paclitaxel at a fixed dose of 175 mg/m² intravenously administered over 3 hours on day 1. UFT and oral leucovorin are given orally for 14 days followed by a 1-week period without treatment. Therapy is repeated every 21 days. UFT is escalated by 100 mg increments from a total starting dose of 300 mg/d while leucovorin is given at a fixed dose of 30 mg three times a day.[39]
Another phase I trial in breast cancer is ongoing.[40]
The current series takes the use of protracted 5-FU application (given orally as UFT) in combination with paclitaxel one step further, applying paclitaxel in a dose-dense and moderately toxic weekly schedule. With 26 patients entered into this new protocol, it is becoming clear that four weekly doses of paclitaxel can be given in combination with full-dose UFT plus leucovorin. The major toxicities appear to be gastrointestinal. One problem of the protracted use of UFT plus leucovorin over 4 weeks might be that gastrointestinal side effects will occur during the last week of oral treatment.

**Conclusions**

Thus, for future protocols, a shortened application schedule may be preferable. However, the goal of this protocol is to establish the maximum tolerated dose and to gain further information regarding phase II data. Promising preliminary responses have been observed in extensively pretreated patients and it is hoped that this study will result in the definition of a tolerable and effective palliative treatment regimen for patients with a variety of solid tumors.

**References:**


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