Paclitaxel (Taxol) is one of the most active drugs in the treatment of ovarian and breast cancers. Combination therapy with paclitaxel and 5-fluorouracil (5-FU) exhibits high activity in anthracycline-pretreated breast cancer.

Introduction

Paclitaxel (Taxol) is a very active agent in the treatment of metastatic breast cancer, yielding single-agent response rates up to 56%, [1] or, in combination with an anthracycline, as high as 80%. [2,3] In these trials, paclitaxel was administered intravenously over 24 or 3 hours—the 24-hour infusion being more common in the United States, and the 3-hour infusion more common in Europe. The shorter infusion schedule is associated with a lower rate of severe myelosuppression; on the other hand, it may produce more peripheral neuropathies. A 1-hour infusion of paclitaxel, offering the added convenience of outpatient treatment, has been investigated in phase I studies. [4] On this schedule, paclitaxel was shown to be safe, with substantial activity in several different tumor types. [4]

Paclitaxel works at the cellular level, [3,5] predominantly impairing dividing cells at the G2/M phase of growth. For this reason, repeated doses are theoretically beneficial, reaching more cells at the susceptible point in the cell cycle. Based on this concept, several clinical trials have examined weekly administration of paclitaxel (Table 1), [6-10] leading to the following conclusions regarding weekly paclitaxel dosing:

- High-dose intensity is possible with weekly administration.
- Hematologic toxicity is mild.
- Long-term treatment with paclitaxel at doses > 100 mg/m² may result in treatment-limiting neurotoxicity.
- Objective response rates are relatively high (30% to 48%).

Anthracycline and alkylating agent-based regimens are used routinely as first-line therapy for metastatic breast cancer. Failure to respond is generally accepted to be a poor prognostic factor for response to available salvage therapy. [11] The development of new combination drug regimens, therefore, has become important to the care of this patient population. In a recent phase I/II study, for instance, combination-therapy with calcium folinate/5-fluorouracil (5-FU)/paclitaxel yielded response rates of 54% to 69% as salvage therapy for anthracycline-resistant breast cancer. [12,13] In this study, 500 mg/m² of calcium folinate was administered as a 2-hour infusion prior to 5-FU at a dose of 2.0 g/m² intravenously over 24 hours; 175 mg/m² of paclitaxel was administered intravenously over 3 hours. All drugs were given on day 1; calcium folinate and 5-FU administrations were repeated weekly on days 8 and 15. The cycle was repeated every 3 weeks. The duration of response was 8 months.

Klaassen et al are currently performing a phase II trial of uracil and tegafur (UFT)/oral calcium folinate (Orzel) plus paclitaxel as second-line treatment of metastatic breast cancer. [14] Patients will receive a single paclitaxel infusion (175 mg/m² over 3 hours) on day 1; UFT plus calcium folinate will be administered three times a day for 14 days, followed by 1 week without treatment. UFT will be escalated in 100-mg increments from a total starting oral dose of 30 mg/day, whereas oral calcium folinate will be administered as a fixed dose at 300 mg three times a day.
Study Objectives

This phase I trial was designed to determine the dose-limiting toxicity, maximum tolerated dose, and recommended dose for phase II testing of weekly paclitaxel administered by 1-hour infusion in combination with UFT/oral calcium folinate for the treatment of patients with anthracycline-resistant metastatic breast cancer. We also wanted to assess early efficacy and safety information on this combination regimen.

Study Design

The study has an open-label, single-center, phase I design. The patient population includes patients with anthracycline-resistant metastatic breast cancer. Premedication consists of dexamethasone 4 mg intravenously, clemastine 2 mg intravenously, and ranitidine 50 mg intravenously administered 30 minutes before paclitaxel. Paclitaxel 80 mg/m² as a 1-hour infusion is administered at 1-week intervals for 6 weeks. Oral UFT/calcium folinate is administered at a starting dose of 200 mg UFT (absolute dose, escalated stepwise to 700 mg total absolute dose in subsequent groups), together with 90 mg calcium folinate on days 1 to 42, followed by a 2-week period without treatment (Figure 1). UFT/calcium folinate is administered orally in three divided doses, 8 hours apart. Depending on tumor response following cycle 1, treatment continues to a maximum of two cycles.

Definition of Dose-Limiting Toxicity

A dose-limiting toxicity is determined by the following hematologic parameters: granulocytes (absolute neutrophil count [ANC]) < 0.5 x 10⁹/L for > 7 days; ANC of < 0.1 x 10⁹/L for > 3 days; any episode of febrile neutropenia, defined as temperature > 38.2°C; granulocytes < 0.5 x 10⁹/L, requiring antibiotics and hospitalization; platelets < 25 x 10⁹/L; bleeding requiring platelet transfusion; or failure of recovery of granulocytes (1.5 x 10⁹/L) and/or platelets (100 x 10⁹/L) by day 57. In addition, any nonhematologic toxicity—common toxicity criteria (CTC) of ≥ grade 3—excluding alopecia and inadequately treated grade 3 vomiting, is considered dose-limiting.

Criteria for Dose Escalation

At least three patients will be treated at each dose level. If none of these patients develops a dose-limiting toxicity during the first cycle, the next dose level may be opened. If one of the first three patients develops a dose-limiting toxicity, a maximum of three additional patients will be treated at this dose level.

Definition of Maximum Tolerated Dose

The maximum tolerated dose will be reached if three of six patients at a given dose level develop a dose-limiting toxicity during any cycle of treatment. The recommended dose for phase II testing will be one dose level below the maximum tolerated dose. Once it has been determined, 10 additional patients will be treated at that dose level.

Conclusion

This phase I trial opened in September 1998. The first patients in dose level 1 tolerated the treatment without problems. At this time, we are not able to provide results from the trial. Results will be available at the end of 1999. The results from recent studies with monotherapy of weekly paclitaxel or UFT/calcium folinate in metastatic breast cancer suggest that the combination may be expected to produce high activity and a low incidence of side effects. This would be an important advance for the population of patients with anthracycline-resistant metastatic breast cancer, who currently have little chance of cure.

References:


Source URL:
http://www.diagnosticimaging.com/review-article/uftoral-calcium-folinate-plus-weekly-paclitaxel-metastatic-breast-cancer

Links:
[1] http://www.diagnosticimaging.com/review-article