UFT/Oral Calcium Folinate Plus Radiation in Pancreatic Cancer

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By Francisco Robert, MD, FACP [2], David Raben, MD [3], and Sharon Spencer, MD [4]

A phase I, single-center, open-label, dose-escalation study (University of Alabama [UAB] 9614) has been undertaken to evaluate the feasibility and safety of uracil and tegafur (in a molar ratio of 4:1 [UFT]) plus oral calcium folinate (Orzel) offers a well-tolerated, fully oral treatment option with efficacy comparable to that of standard 5-FU parenteral regimens.[1,2] Patient acceptance of a noninjected treatment option is likely to be high because this approach frees the patient from the constraints of frequent doctor visits for treatment administration and from the anxiety and discomfort associated with injections. Furthermore, the cost of an oral regimen is expected to be lower than the more labor- and equipment-intensive parenteral treatments, both in terms of direct cost of treatment administration and the indirect cost of lost work days for patients and their families due to treatment visits.

With these benefits in mind, we initiated a phase I study to evaluate the feasibility and safety of administering UFT plus oral calcium folinate in combination with radiotherapy for the treatment of patients with pancreatic cancer.

Introduction

The combination of 5-fluorouracil (5-FU) and radiotherapy appears to be more effective than radiotherapy alone in the treatment of pancreatic cancer. Continuous administration of 5-FU may be superior to bolus treatment in rectal cancer and appears to be promising in pancreatic cancer and other tumor types. Available data suggest that uracil and tegafur (in a molar ratio of 4:1 [UFT]) plus oral calcium folinate (Orzel) offers a well-tolerated, fully oral treatment option with efficacy comparable to that of standard 5-FU parenteral regimens.[1,2] Patient acceptance of a noninjected treatment option is likely to be high because this approach frees the patient from the constraints of frequent doctor visits for treatment administration and from the anxiety and discomfort associated with injections. Furthermore, the cost of an oral regimen is expected to be lower than the more labor- and equipment-intensive parenteral treatments, both in terms of direct cost of treatment administration and the indirect cost of lost work days for patients and their families due to treatment visits.

Rationale

The clinical benefit of administering 5-FU by infusion rather than bolus delivery is based on the short serum half-life of this compound. It is also based on the larger proportion of malignant cells in human solid tumors that are not undergoing active growth, and that are not, therefore, affected by cycle-active antimetabolites at any one point in time. Longer periods of drug administration might result in a greater percentage of tumor cells exposed to the cytotoxic agent during a sensitive phase of the growth cycle, resulting in an enhanced therapeutic effect.

Although the fundamental biochemical mechanism of 5-FU radiosensitization is not well understood, tissue culture experiments[3] have clearly shown that there are three basic prerequisites for 5-FU radiosensitivity: 1) 5-FU must be present after each x-ray exposure; 2) the 5-FU concentration must be sufficient to be cytotoxic from the drug alone; and 3) the duration of 5-FU exposure must be at least one full cell cycle in length. Because of the short half-life of 5-FU in man, these prerequisites can be met only by continuous infusion of 5-FU.

Objectives

The University of Alabama (UAB) study 9614 was designed to determine the maximum tolerated dose and dose-limiting toxicity of UFT plus oral calcium folinate administered three times per day to patients with pancreatic cancer during full-dose radiotherapy. The maximum tolerated dose would then be used to define the appropriate dose for phase II testing. Another goal was to assess the response rate, time to progression, and survival of patients with measurable disease treated in this phase I study setting.

Study Design
In this phase I, single-center, open-label, dose-escalation study, patients with pancreatic cancer are receiving UFT plus oral calcium folinate and concurrent radiation. Dose escalation of UFT will be performed until the maximum tolerated dose is defined. The initial dose of 150 mg/m²/day of UFT was administered with 90 mg/day of oral calcium folinate, both divided into three daily doses for 35 days. Radiotherapy started on day 1 and was administered to a total dose of 45 Gy at 1.8 Gy per day (approximately 5 weeks). UFT doses are being escalated in cohorts of three to six patients (Table 1). The dose and schedule of oral calcium folinate and radiotherapy are being kept constant. No dose escalation will be made during therapy for individual patients.

In the second part of this study, an additional group of six patients will be treated at the recommended phase II dose, which will be one level lower than the maximum tolerated dose of UFT plus oral calcium folinate. This approach will provide some early information on efficacy and will expand our knowledge of the toxicity profile of this combined-modality regimen.

**Preliminary Results**

A total of 11 patients with a median age of 59 years have been accrued into this study. The patients have been treated with UFT at doses of 150 to 300 mg/m²/day. The first three cohorts of patients (150 mg/m²/day, 200 mg/m²/day, and 250 mg/m²/day) included three patients at each dose level. Currently, two patients have completed therapy at dose level 4 (300 mg/m²/day). Overall, therapy has been well tolerated, and the maximum tolerated dose has not yet been reached.

**References:**


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