Tegafur/Uracil + Calcium Folinate in Colorectal Cancer
Double Modulation of Fluorouracil

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Abstract
The oral chemotherapeutic agent tegafur/uracil (UFT®) is the first of a new class of anticancer drugs called dihydropyrimidine dehydrogenase inhibitory fluoropyrimidines. Tegafur/uracil combines uracil with the fluorouracil prodrug tegafur in a 4:1 molar ratio. Uracil competitively inhibits the degradation of fluorouracil, which results in the concentration of fluorouracil remaining at sustained levels in both plasma and tumour. Tegafur/uracil has been commercially available in Japan since 1983 and examined extensively in various tumours. Trials conducted in the US have focused on the combination of tegafur/uracil plus calcium folinate (calcium leucovorin) [ORZEL®]. Several phase I and II trials have evaluated the maximum tolerated dose, pharmacokinetics, efficacy, and safety of this combination in the treatment of colorectal cancer. Results have shown that tegafur/uracil at 300 mg/m²/day in divided doses given every 8 hours for 28 days provides prolonged exposure to fluorouracil. Furthermore, tegafur/uracil + calcium folinate is well tolerated, with dose-limiting toxicity manifesting as diarrhoea. Compared with intravenous fluorouracil plus folinic acid (leucovorin) regimens, tegafur/uracil + calcium folinate has similar efficacy with less toxicity and is more convenient because it is an oral regimen. Early studies have also shown potential cost savings because of fewer complications.

Colorectal cancer is the third leading cause of cancer mortality in males and females in the US, with an estimated 131 600 new cases and 55 500 deaths in 1998.1 Even though the majority of tumours are surgically resectable at the time of diagnosis, disease in more than 50% of these patients will recur and require further treatment.

Fluorouracil is the most widely prescribed antineoplastic drug for the treatment of advanced colorectal cancer and is currently the only recommended agent for use as adjuvant chemotherapy in stage II and III disease.2 It is primarily given as an intravenous infusion and frequently combined with folinic acid (leucovorin), which acts as a biochemical modulator of fluorouracil. Some studies have suggested that a prolonged fluorouracil infusion results in superior response rates and may even increase median survival compared with that produced by bolus fluorouracil regimens.3-5 However, protracted intravenous infusions may be expensive because they require the insertion of central intravenous catheters and the use of portable infusion pumps. In addition, catheter-related complications of venous thrombosis, catheter slippage, and infection can be noted in 30% of patients, requiring catheter replacement in 11% of...
all patients. An oral regimen that provides continuous fluorouracil exposure for prolonged periods of time without such complications would be an improvement over existing treatments.

1. History of Tegafur/Uracil

Synthesised more than 30 years ago by Hiller et al.,[7] tegafur is a prodrug of fluorouracil. Initial trials of tegafur in the US evaluated short-duration intravenous dosages, which resulted in high peak plasma concentrations of tegafur and fluorouracil but unacceptable toxicity. Toxic reactions consisted of myelosuppression, diarrhoea, and central nervous system toxicity. This unfavourable toxicity profile led to the abandonment of tegafur development in the US for more than 2 decades.[8-10]

In contrast to the US experience, Japanese investigators used low dose oral schedules of tegafur over prolonged periods and obtained moderate efficacy in gastric, colon, and breast cancers, with minimal neutropenia and oral mucositis observed.[11,12] Tegafur/uracil (UFT®) is an oral antineoplastic drug that combines uracil and tegafur in a 4 : 1 molar ratio.[13,14] Fluorouracil is generated from tegafur and is subsequently modulated by uracil, which in vitro competitively inhibits the enzyme dihydropyrimidine dehydrogenase (DPD).[15,16] Tegafur/uracil is therefore the first in a new class of anticancer agents called DPD inhibitory fluoropyrimidines. Since early 1980, tegafur/uracil has been largely studied in, and used to treat, solid tumours in Japan,[17] where it was approved in 1983 for use in a variety of solid tumours. In 1990 US investigators initiated phase I trials of single agent tegafur/uracil,[18] with subsequent phase I trials combining tegafur/uracil with oral calcium folinate (calcium leucovorin) [ORZEL®] in attempts to biochemically modulate the fluorouracil generated from tegafur/uracil by calcium folinate.[19] Treatment with tegafur/uracil + calcium folinate therefore provides dual-modulated fluoropyrimidine therapy, i.e. modulation by both uracil and calcium folinate.

2. Pharmacology

Tegafur is slowly metabolised to fluorouracil, primarily by the hepatic microsomal cytochrome P450 pathway.[20] The resultant agent has the same metabolism and cytotoxic activity as intravenous fluorouracil. In vivo, fluorouracil is metabolised to 2 active nucleotides: fluorodeoxyuridine monophosphate, which forms a complex with thymidylate synthase that affects DNA synthesis, and fluorouridine triphosphate, which is integrated into cellular RNA and may alter its processing and function.[12,21,22] As hypothesised, tegafur/uracil produced higher concentrations of fluorouracil in breast and gastric tumours than did single agent tegafur.[23,24] In addition, increased antitumour activity, characterised by increased response rates, was also demonstrated.[25,26]

The modulation of fluorouracil by calcium folinate is characterised by the stabilisation of the fluorodeoxyuridylate-thymidylate synthase covalent ternary complex in the presence of 5,10-methylene tetrahydrofolate. This modulation increases inhibition of the enzyme thymidylate synthase in the DNA synthetic pathway, which enhances the cytotoxic activity of fluorouracil.[21,27-29] Uracil and calcium folinate provide a double modulation of the fluorouracil generated from tegafur. This combination has been demonstrated to be superior to tegafur/uracil alone in rats bearing subcutaneous advanced colorectal tumours,[27] and to increase the degree of thymidylate synthase inhibition in patients with gastric cancer.[30]

3. Pharmacokinetics

Initial phase I studies evaluated the pharmacokinetics of tegafur, uracil, and fluorouracil after administration of tegafur/uracil to 21 patients with solid tumours (Dr D.H. Ho, University of Texas M.D. Anderson Cancer Center, personal communication). Two schedules were studied: a 5-day course with doses starting at 360 mg/m²/day and escalating to 900 mg/m²/day, and a 28-day course with doses starting at 180 mg/m²/day and escalating to 450 mg/m²/day. The total daily dose was