Impact of UFT on Tumoral TS and DPD Levels in Colorectal Cancer

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This was an open label, pilot translational clinical pharmacology study of a brief (7 day) course of UFT, 300 mg/m²/day, in combination with leucovorin, 90 mg/day, in six patients with newly diagnosed advanced colorectal cancer.

Introduction

UFT is an active anticancer drug in patients with colorectal cancer.[1] UFT is composed of a fixed molar ratio (1:4) of tegafur and uracil. In this pilot study, with a translational clinical pharmacology design, previously untreated patients with advanced colorectal cancer (Table 1) were treated with UFT plus oral leucovorin (a combination being developed under the trade name Orzel). Patients were treated for 7 days with UFT (300 mg/m²/d) plus leucovorin (90 mg/d) in three daily doses. The patients enrolled in this study were candidates for partial or total resection of tumor. Tumor and blood samples were obtained less than 1 week before drug administration and within 1 to 4 hours after the last drug intake (at time of tumor resection). Approval was obtained from the local ethics committee and all patients gave informed consent.

Thymidylate synthase (TS) levels were determined by a slightly modified FdUMP binding assay,[2] and dihydropyrimidine dehydrogenase (DPD) activity was determined by radioenzymatic assay, using (14C) fluorouracil (FU) as substrate.[3,4] Drugs and metabolites were measured by gas chromatography and mass spectrometry (5-FU, m/z = 301; uracil, m/z = 283; fluoro-β-alanine [FBAL], m/z = 278) or by high-performance liquid chromatography (tegafur).

Results

Table 2 shows the impact of the 7-day UFT treatment on tumor thymidylate synthase levels (FdUMP binding) and dihydropyrimidine dehydrogenase activity. The rate of tumoral inhibition after the 7-day UFT treatment sequence varied between 5% (patient 5) and 31% (patient 4). UFT treatment induced a systematic decrease in tumor dihydropyrimidine dehydrogenase activity ranging from 13% (patient 4) to 60% (patient 3). In comparison, the changes in lymphocytic dihydropyrimidine dehydrogenase activity were less consistent (only three of six patients exhibited a marked decrease after UFT treatment).

Table 3 illustrates the patient-to-patient variations in drug concentrations. UFT treatment induced a systematic increase in uracil concentrations both in plasma and tumors. Tegafur, 5-FU, and FBAL were found in plasma and tumors at variable concentrations; the highest drug concentrations were those of FBAL in plasma.

Conclusions

This pilot study demonstrated that a short, 7-day sequence of UFT treatment is able to induce measurable and variable effects on thymidylate synthase intratumor activity, resulting in 5% to 31% occupation of thymidylate synthase binding sites and a 13% to 60% decrease in intratumor dihydropyrimidine dehydrogenase activity. Drug and metabolite concentrations were detected at variable levels in both plasma and tumor, with FBAL exhibiting the highest concentrations in plasma.

References:


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