Although the combination of uracil and tegafur (UFT) has been available commercially in Japan since 1984 and is one of the most extensively prescribed antineoplastic agents in that country, few physicians outside Japan have knowledge of and experience with the drug. The development of UFT, which combines uracil and tegafur in a 4:1 molar concentration, dates back to the pioneering work of Fujii in the late 1970s and is based on the observation of uracil's ability to inhibit the degradation of fluorouracil (5-FU) generated from tegafur.[1] This was an early example of biochemical modulation, with uracil inhibiting the enzyme dihydrouracil dehydrogenase and thus prolonging plasma 5-FU levels and increasing 5-FU distribution to tumors compared with normal tissues.[2]

To understand the development of UFT, one must view the differences in drug development philosophies between the United States and Japan historically. In the United States, tegafur—the cytotoxic component of UFT—their was studied in the 1970s by the National Cancer Institute in clinical trials using primarily intravenous dosing schedules of short duration that yielded high peak plasma levels of tegafur and 5-FU.[3] Objective responses were observed in patients with colorectal, breast, and gastric cancers, but severe diarrhea, mucositis, and central nervous system toxicity complicated therapy. Development of tegafur was halted in the United States due to this drug's greater toxicity and seeming lack of therapeutic advantage over 5-FU.

**Prolonged, Oral Dosing**

By contrast, in Japan tegafur was administered using prolonged oral dosing schedules. The aim—different from that in US trials—was to deliver the drug at relatively low doses but over prolonged periods, with few interruptions.[4] Interestingly, this concept was later discovered in the United States, with the advent of protracted low-dose intravenous 5-FU infusions.[5] The commitment to oral tegafur in Japan led investigators to document its activity in a variety of tumors, including breast, head and neck, and gastrointestinal cancers, and its mild toxicity when administered orally at low doses over long periods. Recognition of uracil's action on 5-FU metabolism subsequently led to the development of UFT.[1-4]

Many early Japanese trials of UFT, performed in the 1970s and early 1980s, did not use the conventional toxicity criteria, definitions of maximum tolerated dose, dose escalation protocols, and standardized response criteria carefully defined by US investigators over the last two decades. Therefore, US investigators began phase I studies of UFT in 1990, even though the drug was available commercially in Japan. In addition, leucovorin, a biochemical modulator of intravenous 5-FU that had been prescribed increasingly in the United States, had not been studied in Japan with either intravenous 5-FU or UFT.[6]

**A Bridge Between Two Drug Development Strategies**

The current development of UFT with leucovorin represents a bridging of Japanese and US drug development philosophies. The use of a prolonged oral dosing of UFT, consistent with an emerging belief that protracted schedules may be the preferred means of administering intravenous 5-FU,[7] originated in Japanese trials. Administration of UFT at or near the maximum tolerated dose is consistent with US phase I trial methodology, and recognizes that the optimal dose intensity of prolonged oral dosing is achieved only by minimizing toxicity-related dose interruptions. Extensive experience from US trials with the biochemical modulation of 5-FU by leucovorin led to an oral treatment regimen in which leucovorin modulates the 5-FU generated from UFT.

Development of the UFT plus leucovorin regimen has concentrated on a 28-day administration schedule because of the encouraging objective response rates and mild toxic effects observed in phase II testing of this schedule.[8] In contrast to bolus 5-FU schedules, the oral schedule did not appear to induce significant neutropenia, oral mucositis, alopecia, or toxicity-related hospitalizations. Moreover, unlike protracted intravenous infusion of 5-FU, the oral schedule did not require costly
infusion pumps or insertion of central venous catheters with the attendant problems of line slippage, infection, and thrombosis.

Studies in Spain also combined UFT with oral leucovorin, noting impressive antitumor activity and a mild toxicity profile in a variety of tumor types, including colorectal, gastric, and breast cancer.[9,10] These investigators demonstrated the value of UFT plus leucovorin in clinical situations in which palliative therapies having mild toxic effects may be especially important, such as those involving heavily pretreated breast cancer patients or elderly patients with metastatic colorectal cancer. The successful clinical application of an oral treatment with a prolonged administration time requires collaboration among the physician, nurse, and patient. The patient must be educated about the importance of compliance and the management of diarrhea, the dose-limiting toxicity associated with administering a UFT plus leucovorin regimen. In the presence of early-stage diarrhea, simply eliminating several UFT doses can prevent the diarrhea from progressing to a serious or life-threatening toxicity.

The conference proceedings presented herein bring clinicians from Japan, Europe, and the United States together to discuss their experiences in past clinical trials and to focus collectively on new directions in the use of this novel oral therapy.

References:


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