Question: Why does UFT® produce diarrhea but not stomatitis?
Dr. Pazdur: It appears that FT may be converted to fluorouracil (5-FU) in the GI mucosa. This mechanism is likely the cause of the diarrhea.

Question: The recommended adjuvant chemotherapy for colorectal cancer is that of 5-FU on a weekly basis and levamisole every 2 weeks for 1 year. Has any study been conducted that examines the replacement of weekly 5-FU with UFT®?
Dr. Pazdur: No such study has yet been conducted. Obviously, we are at a preliminary point in the development of UFT® in the United States. UFT® is an attractive drug in this setting. It is available in oral form and does not produce neutropenia. For this reason, the NSABP will prospectively randomize 1,500 Dukes’ B and C colon cancer patients to receive either our 28-day treatment regimen of UFT® plus oral leucovorin or weekly intravenous 5-FU and leucovorin. The duration of both treatments is 6 months.

Question: Does liver impairment affect the efficacy of UFT®?
Dr. Rustum: It is unlikely that limited liver impairment will affect the efficacy of UFT®, with the exception of jaundice, which is a contraindication for this drug.

Question: Given that the standard of living in Thailand is about the same as that in the Philippines, would you address the issue of whether 5-FU or UFT® is more economical?
Dr. Villalon: 5-FU must be given by a doctor in a hospital setting. In the Philippines, this is a problem because of geography and few cancer centers. Therefore, although UFT® may be more expensive, it can be administered by private practitioners in the provinces, thus relieving patients of the burden of travel and expense in reaching a major center for hospital care. Fluorouracil causes leukopenia and therefore increases the probability of infection. Hospitalization, antibiotics, and colony-stimulating factors add to the expense of treating infections caused by 5-FU treatment. Oral UFT® does not cause leukopenia. In the end, the benefits of UFT® may outweigh the additional cost.

Question: In the trial conducted with breast cancer, only 2 patients had diarrhea. Is this due to the site? That is, if the tumor is in the colon, is absorption affected? Or does the addition of leucovorin to UFT® produce more diarrhea?
Dr. Pazdur: The latter is correct. If you combine any of the fluorinated pyrimidines, whether it be UFT® or 5-FU, with leucovorin, the dose of UFT® or 5-FU must be reduced. Greater toxicity is associated with the addition of leucovorin.

Question: Is there a difference between administering UFT® on a b.i.d. or t.i.d. basis or on a 14-day versus a 28-day schedule?
Dr. Pazdur: We examined a 14-day schedule, administering UFT® three times daily. The maximum tolerated dose was 350 mg/m²/day, with diarrhea being the dose-limiting toxicity. It does not seem possible to increase the dose beyond that. As for the number of daily doses, I do not know whether twice daily is preferable to three times daily. However, if one is attempting to develop a therapy to resemble a protracted administration schedule of 5-FU, it seems reasonable...
to administer UFT® every 8 h since the serum levels of 5-FU disappear 8 h after oral administration. An excellent study performed in Spain by Dr. Gonzalez-Baron and associates administered UFT® plus leucovorin on a b.i.d. schedule and obtained similar results to our US study.

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With regard to the pharmacoeconomics of UFT®, a major objective of our phase III trial is to compare the costs of intravenous 5-FU/leucovorin for 5 days versus UFT®/oral leucovorin. Perhaps the most important issue to examine is toxicity-related hospitalizations. One or two toxicity-related hospitalizations in the United States is extremely costly and outweighs any pharmacy-related cost. As our health care system changes, we must consider the total cost of drug delivery. Therefore, oral treatment becomes very advantageous because it eliminates the need for patients to return every day for 5 days to receive intravenous 5-FU and leucovorin. Although formal quality of life studies were not performed with our phase II trials of UFT plus oral leucovorin, our patients tolerated therapy very well. Patients were able to maintain active work schedules with minor inconveniences to daily living activities. This therapy will be particularly advantageous to older patients to whom physicians may be reluctant to administer therapies with significant toxicities.

Question and Answer Session
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