Researchers, primarily in Japan, Europe, and the United States, have evaluated several new fluorinated pyrimidines in recent years. Most of these drugs are orally active prodrugs of fluorouracil (5-FU), and some also contain biochemical modulators of 5-FU. Two of these prodrugs, S-1 and BOF-A2, have shown promising preliminary results. This article summarizes the preclinical and clinical development of S-1 and BOF-A2.

**S-1**

**Pharmacology and Preclinical Evaluation of S-1**

S-1 is a combination of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (potassium 1,3,5-triazine-2,4(1H,3H)-dione-6-carboxylate) at a fixed molar ratio of 1:0.4:1. Tegafur (5-fluoro-1-(tetrahydro-2-furanyl)-2,4-(1H,3H)-pyrimidinedione), a prodrug of 5-FU, was developed in the former Soviet Union and introduced in 1967.[3] Evaluation of tegafur in the 1970s by the United States National Cancer Institute revealed that, when administered by short intravenous infusion, the drug caused significant gastrointestinal and neurologic toxicity despite demonstrated activity in a variety of solid tumors.[4,5] Because tegafur is well absorbed via the oral route, Japanese investigators pursued an alternative strategy of prolonged oral administration. Further development of tegafur took place mainly in Japan, although researchers in the United States conducted additional phase I and II studies of oral tegafur.[6,7]

The development of S-1 represents a rational approach to the pharmacologic modulation of fluoropyrimidines.[8] After being absorbed by the gastrointestinal tract, tegafur is converted to 5-FU by the hepatic microsomal enzyme system.[9] CDHP reversibly inhibits dihydropyrimidine dehydrogenase (DPD), the chief enzyme regulating 5-FU degradation. In vitro, CDHP is almost 200 times more potent than uracil, another reversible inhibitor of DPD.[10] When CDHP is combined with tegafur, the resulting 5-FU levels are maintained both in plasma and in tumor tissue.[8]

**Gastrointestinal Toxicity**

Early research attributed the gastrointestinal toxicity of 5-FU to its phosphorylation.[11] In animal models, potassium oxonate inhibits the activity of orotate phosphoribosyltransferase, the enzyme that catalyzes 5-FU phosphorylation in the gastrointestinal tract, thus leading to decreased gastrointestinal toxicity without loss of antitumor activity.[12]

Researchers in Japan conducted preclinical evaluation of S-1 and demonstrated its antitumor activity in experimental models of rodent tumors and human xenografts. S-1 significantly inhibited tumor growth in rats with subcutaneous Yoshida sarcoma[13], and in rats and nude mice orthotopically implanted with human colon cancer cell lines.[14,15] The animal studies also confirmed that the gastrointestinal toxicity of S-1 is low, most likely because of the protection afforded by potassium...
Pharmacological data derived from these studies indicated high concentrations of 5-FU in the plasma and tumor tissue of animals treated with oral S-1. In addition, S-1 compared favorably with intravenous 5-FU, showing similar levels of tumor inhibitory activity and gastrointestinal toxicity.[16]

**Phase I Studies of S-1**

Phase I trials of S-1 have been conducted in Japan, Europe, and the United States. Japanese investigators administered S-1 for 28 consecutive days, followed by a 14-day rest period. In a phase I study using two dosing schedules of S-1, Taguchi et al identified the maximum tolerated doses as 75 to 100 mg twice daily or 150 to 200 mg once daily.[17] Toxicity was mainly hematologic, and gastrointestinal side effects were generally mild.

In another phase I study, Hirata et al treated 12 patients with fixed doses prespecified according to body surface area.[18] Patients with a body surface area < 1.25 m$^2$ received 40 mg twice daily; those with a body surface area of 1.25 to 1.5 m received 50 mg twice daily; and those with a body surface area > 1.5 m received 60 mg twice daily. Dose escalation was not included in the protocol of this study; rather the primary objective was to investigate the pharmacokinetics of S-1. The only grade 3 or 4 toxicity was hematologic and occurred in three patients.

**Dosing Based on Actual Measurement vs Body Surface Area**

Phase I studies of S-1 conducted in Europe and the United States employed a dosing schedule based on actual body surface areas. The European Organization for the Research and Treatment of Cancer (EORTC) reported the preliminary findings of a phase I study of S-1. Fifteen patients received the drug for 28 days, followed by a 7-day rest period. The starting dose was 25 mg/m$^2$ twice daily, and dose-limiting toxicity was reached, at 45 mg/m$^2$ twice daily. Although the Japanese study reported only mild gastrointestinal side effects, the EORTC data identified grade 3 or 4 diarrhea as the primary dose-limiting toxicity.[19] An analysis of 13 of 28 patients receiving 25, 35, 40, or 45 mg/m$^2$ once daily showed linear pharmacokinetics for S-1 components, such as 5-FU and CDHP, and for endogenous uracil.[20]

We, at The University of Texas M. D. Anderson Cancer Center, conducted a phase I study of S-1 administered for 28 days, followed by a 7-day rest period.[21] Consecutive cohorts of patients received escalating doses of S-1. The starting dose of 30 mg/m$^2$ twice daily was found to be the maximum tolerated dose, and, as in the EORTC study, diarrhea was the dose-limiting toxicity. In contrast to the findings of the Japanese study, our study documented infrequent hematologic toxicity. The pharmacokinetic profiles of S-1 constituents suggested linear kinetics, and measurement of endogenous uracil confirmed the transient nature of DPD inhibition.

**Phase II Studies of S-1**

Phase II studies of S-1 conducted in Japan used a fixed-dose schedule adjusted to the ranges of body surface areas. Three trials among patients with advanced gastric cancer were reported. In a study of 51 patients with no history of previous chemotherapy, Sakata et al documented an objective response rate of 49%.[22] In a second study, reported in abstract form, 50 patients evaluable for efficacy demonstrated an overall response rate of 40%, confirming the activity of S-1 in advanced gastric cancer.[23]

Sugimachi et al treated 28 patients, of whom 9 had received previous chemotherapy. Objective responses, documented in 12 of 23 patients (52%) with measurable disease, did not differ, irregardless of whether patients had or had not received prior chemotherapy.[24] Based on the good results observed in patients with advanced gastric cancer treated with S-1, the drug received approval for this indication in Japan.

The EORTC Early Clinical Studies Group has launched an early phase II study of S-1 in patients with advanced/metastatic gastric and colorectal cancer. It recently reported that a patient with gastric
cancer who could only tolerate only one cycle of S-1 therapy experienced a durable complete pathologic response in the primary tumor, with stable metastatic disease.[25] Although anecdotal, the experience with this patient clearly illustrates the activity of the drug and suggests that it should be evaluated further in disease-specific settings.

Phase II studies of S-1 in patients with other types of solid tumors have yielded promising results. S-1 produced an overall response rate of 36% in 62 patients with previously untreated, advanced colorectal cancer.[26] In another trial of S-1 in 29 patients with measurable advanced colorectal cancer, only 4 (14%) responded. However, in the latter study, 25% of patients (4 of 16), who had not received prior chemotherapy, achieved a partial response.[24] S-1 produced objective responses in 41% of 27 evaluable patients with advanced breast cancer,[27] and in 46% of 26 evaluable patients with advanced head and neck tumors.[28]

**Predominant Toxicities**

In all the phase II studies summarized above, the predominant toxicities were hematologic and included anemia and neutropenia. These studies report only a few cases of grade 3 or 4 diarrhea or stomatitis, and infrequent incidences of other gastrointestinal toxicities. However, diarrhea of any grade was documented in 24.1% of the 144 patients participating in the studies.[24] In another study, grade 1 or 2 stomatitis was seen in 23.5% of patients, and grade 1 nausea/vomiting occurred in 11.7%.[22]

The differences between the toxicity profiles observed in the Japanese studies (in which toxicity was chiefly hematologic) and the EORTC and the M. D. Anderson Cancer Center studies (in which diarrhea was the dose-limiting toxicity and hematologic toxicity was mild) remain unexplained. Evidence suggests that the conversion of tegafur to 5-FU occurs more slowly in Asians than in other ethnic groups, a finding that seems to be confirmed by a comparison of our pharmacokinetic data with the data obtained from the Japanese trials.[18,21]

**BOF-A2**

In the search for biochemical modulators of the activity of 5-FU, Japanese investigators have described the activity of 1-ethoxymethyl-5-fluorouracil (EM-FU), another prodrug of 5-FU, and 3-cyano-2,6-dihydroxypyridine (CNDP), a potent inhibitor of DPD.[29] Like tegafur, EM-FU is converted to 5-FU by the hepatic microsomal enzyme system.[30] In vitro, CNDP is approximately 300 times more potent than uracil in inhibiting DPD.[10] BOF-A2, a molecule that combines EM-FU and CNDP in equimolar ratios, spontaneously degrades to the parent compounds in vivo.

Early preclinical data suggested the presence of long-lasting serum levels of 5-FU after oral administration of BOF-A2 to rats. In addition, these animals had high concentrations of 5-FU in tumor tissue.[30] The antitumor activity of oral BOF-A2 was demonstrated in rodent sarcoma models[30] and in several human cancer xenografts.[31-33]

In a phase II study of BOF-A2 conducted in Japan, the drug was administered orally at a dose of 200 mg twice a day for 2 weeks, followed by a 2-week rest period.[34] Sixty-five patients with non-small-cell lung cancer were treated and evaluated for toxicity, and more than 90% of the planned doses were delivered. Reported rates of side effects with this regimen were modest, with grade 3 or higher complications seen in less than 7% of patients.

The incidence of grade 2 or higher diarrhea was 9%; stomatitis, 11%; anemia, 6%; leukopenia, 8%; and thrombocytopenia, 8%. Two additional patients discontinued therapy during the first cycle due to grade 1 or 2 gastrointestinal symptoms. Among the 62 patients evaluable for efficacy, 11 patients (18%) demonstrated partial responses, and 34 patients (55%) achieved stable disease.

**Conclusions**

Oral fluorinated pyrimidines are an attractive alternative to intravenous 5-FU. Pharmacologic modulation offers not only patient convenience, but also the potential for enhanced efficacy of the
parent compound. S-1 and BOF-A2 are two active agents with demonstrated activities under evaluation in preclinical solid tumor models and in early clinical studies.

Questions and Answers

Peter O’Dwyer, MD: For the S1, that ethnic difference in toxicity is pretty interesting. Is there any evidence that oxonic acid is less effective in European populations than in the Japanese population?

Paulo Hoff, MD: This is obviously a subject of great debate. Comparing the data that we have from Japan and our own pharmacogenetics, oxonic acid absorption, at least, does not seem to be significantly different. Dr. Tagouchi has been very interested in this, and he believes that the difference is in the hepatic microsomal system, that the Japanese will have a different rate of conversion from tegafur to the 5-FU and this will allow them to get a higher dose and less toxicity.

Peter Danenberg: Bob Diasio found that there are a certain number of patients with very low DPD to whom 5-FU is very toxic, and when they add these DPD inhibitors, they’re just thrown in indiscriminately without knowing the DPD levels in the patient. So with somebody who was low to begin with, do you ever see an occurrence of [AU: UNCLEAR, BUT SOUNDS LIKE “DPD INHIBITION IN REVERSE.”].

Dr. Hoff: No. We don’t.

Robert Diasio, MD: There’s a theory that basically you could level the playing field by making everybody essentially DPD deficient by administering a small dose of 5-FU.

Leonard Saltz, MD: It’s somewhat equivalent to the concept of the higher dose of leucovorin. It’s leveled the playing field by getting everybody up to a certain higher saturated level of these folates. [AU: "FOLATES" CORRECT?] Effectively, what we’re doing is making everybody into a DPD deficient patient; that’s okay, as long as you know that in advance and dose accordingly.

Dr. Hoff: It’s interesting to note that with these large trials, we haven’t had anybody die from DPD deficiency. So the theoretical concern is there, but the practical point is if you have a 3% incidence of DPD deficiency, you would have probably seen a problem in the large trials.

Dr. Saltz: It’s a little hard to know.

Dr. Diasio: The issue of oral drugs in upper GI malignancies seems like a confounding problem in terms of people taking things orally. This concept of oral drugs and the lack of knowledge of their absorption is especially true with pancreatic cancer, for example, where you have a hard time getting patients to eat.

Dr. Hoff: We know that the drugs are absorbed in the duodenum and proximal jejunum. So, I guess as long as you have small bowel intact, you can use them, and they get through. Obviously, the issue of the pancreatic cancer is an interesting one.

Dr. Saltz: In the Japanese gastric studies, what were the criteria for response?

Dr. Hoff: They used the standard Japanese criteria, which are very different than ours[using a combination of endoscopies and scans. The 53% response rate they had was using the Japanese definition of response, not the conventional Western definition, and that’s why it’s so hard to understand and apply their data here.

References:


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