The Oral Fluorouracil Prodrugs

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Discussion herein are selected oral fluorinated pyrimidines that are converted to 5-fluorouracil (5-FU) in vivo to exert antitumor activity. These agents include capecitabine (Xeloda), tegafur-uracil (UFT) plus leucovorin (Orzel), and S-1 (BMS247616). These agents offer the convenience of an orally administered therapy with potentially fewer toxic effects than conventional bolus regimens of 5-FU plus leucovorin. These agents provide prolonged 5-FU exposure at lower peak concentrations than observed with bolus intravenous administration of 5-FU and may confer pharmacoeconomic advantages by reducing administration costs and toxicity-related hospitalizations. These regimens also have the potential for improved therapeutic activity by achieving higher 5-FU concentrations in the tumor or by biochemically modulating 5-FU. Phase III trials in patients with advanced colorectal carcinomas are comparing the antitumor activity of these agents with that of intravenous 5-FU plus leucovorin. [ONCOLOGY 12(Suppl 7):48-51, 1998]

Introduction

Although 5-fluorouracil (5-FU) remains the most active single agent in the treatment of metastatic colorectal cancer, less than a third of patients achieve objective responses.[1] The use of permanent venous-access devices and portable infusion pumps have allowed continuous infusion of 5-FU over prolonged periods. Compared with bolus schedules, protracted infusions of 5-FU are associated with less toxicity, improved response rates, and the suggestion of improved survival.[2,3] Clinical trials exploring the biochemical modulation of 5-FU by calcium leucovorin have demonstrated improved response rates.[4] Significant toxic effects, primarily diarrhea, mucositis, and neutropenia have been observed. Approximately 20% to 30% of patients require hospitalization for the treatment of these effects, which contribute to a decrement in quality of life and personal comfort and increase the expense of palliative treatment.[5]

In addition to the treatment regimen of eniluracil and oral 5-FU, which is discussed elsewhere in this journal, oral fluorinated pyrimidines under general development for the treatment of colorectal carcinoma, including capecitabine (Xeloda), UFT plus leucovorin (Orzel), and S-1 are reviewed herein. The goal of each of these products is to provide prolonged tumor exposure to therapeutic levels of 5-FU. Each, however, employs a unique mechanism of action to accomplish this goal and potentially to improve therapeutic efficacy of 5-FU. Oral 5-FU has not gained widespread clinical acceptance because of its erratic absorption due to the varying levels of dihydropyrimidine dehydrogenase (DPD) in the gastrointestinal tract.[6] The 5-FU prodrugs have been developed to circumvent this problem. These drugs are absorbed as intact molecules and are subsequently converted to 5-FU to exert antitumor activity. Because these oral agents provide prolonged 5-FU exposure at lower peak concentrations than those observed with bolus intravenous administration of 5-FU, toxic effects such as neutropenia and stomatitis are greatly reduced. In addition, preclinical studies have suggested that these oral agents have potential advantages over intravenous 5-FU, which may increase therapeutic efficacy.[7-10]

Capecitabine

Capecitabine was developed as a tumor-selective fluoropyrimidine carbamate to achieve higher intratumoral 5-FU levels and less toxicity than 5-FU (Figure 1). Capecitabine passes unchanged through the gastrointestinal tract and is metabolized in the liver by carboxylesterase to 5'-deoxy-5-fluorocytidine (5'-DFCR). This is then converted to doxifluridine (5'-DFUR) by cytidine deaminase located in the liver and also in tumor tissue. Lastly, 5'-DFUR is metabolized by thymidine phosphorylase to 5-FU at the tumor site.[7,11] The exposure of healthy body tissues to systemic 5-FU is therefore reduced. Preclinical studies have demonstrated capecitabine's activity in both...
5-FU-sensitive and 5-FU-resistant tumors.[12] In xenograft models, concentrations of 5-FU were found to be higher in tumor than in plasma or healthy tissue following capecitabine administration.[11] Phase I trials of capecitabine in patients with advanced or metastatic solid tumors explored continuous and intermittent schedules with and without oral leucovorin. Dose-limiting toxicities included diarrhea, nausea, vomiting, and hand-foot syndrome.[13-15] Capecitabine’s pharmacokinetics in the above phase I studies demonstrated absorption of at least 70% of capecitabine followed by extensive and rapid conversion to 5’-DFCR and 5’-DFUR. The peak plasma concentrations of the drug and these metabolites occur within 0.5 to 1.5 hours after administration. At the maximum tolerated dose, the average plasma concentrations are similar to those reported for protracted low-dose intravenous 5-FU infusions.[16] Tumor selectivity was studied in 19 patients with colorectal cancer requiring surgical resection of primary tumor and/or liver metastasis. Patients received capecitabine twice daily for 5-7 days prior to surgery. Concentrations of 5-FU in primary tumors were 2.5 times greater than those measured in adjacent healthy tissues, and 1.17 times greater in liver metastasis than in noncancerous liver tissue. Concentrations of 5-FU were 14-fold greater in primary tumors than in plasma. In liver metastases, the ratio in tumor to plasma approximates 8:1. These results strongly suggest that 5-FU in tumor is generated in the tissue by the conversion of 5’-DFUR to 5-FU via thymidine phosphorylase, rather than from the systemic circulation.[17] A randomized open-label phase II trial of three schedules of capecitabine (continuous, intermittent, and intermittent with leucovorin) in patients with metastatic colorectal cancer demonstrated that all treatment groups had similar response rates (21% to 24%). The median time to disease progression was 230 days, 127 days, and 165 days, respectively. The addition of leucovorin to the intermittent schedule neither increased the overall response rate nor elicited a discernible delay in the median time to disease progression.[18] The intermittent schedule (capecitabine 2,500 mg/m² in two divided doses daily for 2 weeks followed by 1 week rest) was selected for further development in colorectal cancer. Phase III trials in patients with advanced colorectal carcinoma are comparing the intermittent capecitabine schedule to intravenous 5-FU plus leucovorin and examining efficacy parameters of tumor response, time to disease progression, and survival, as well as quality of life and pharmacoeconomic resource utilization.

**UFT Plus Oral Leucovorin**

Tegafur, a prodrug of 5-FU, is hydroxylated and converted to 5-FU by hepatic microsomal enzymes; this may lead to a gradual but sustained level of 5-FU in tumors. Japanese clinical trials using oral, divided-dose schedules of tegafur demonstrated its clinical efficacy with mild toxic effects. Uracil was then added to tegafur, which led to the subsequent development of UFT (Figure 2). Uracil biochemically modulates 5-FU by completely inhibiting dihydropyrimidine dehydrogenase (DPD), leading to increased and sustained levels of 5-FU.[19] Schedule-dependent toxic effects were noted in US trials examining UFT as a single agent in 5- and 28-day schedules; the dose-limiting toxicities were neutropenia and diarrhea, respectively.[20] Initial US phase I trials of UFT plus oral leucovorin examined an administration schedule of 28 consecutive days repeated every 35 days. Daily doses of both drugs were divided and administered every 8 hours. The dose-limiting toxicity was diarrhea; the recommended phase II dose was UFT 300 to 350 mg/m²/day plus leucovorin 150 mg/day.[21] Pharmacokinetic studies of UFT plus oral leucovorin administered every 8 hours demonstrate that 5-FU levels can be measured throughout the 8-hour period between doses. Studies of single-dose UFT demonstrate that uracil, tegafur, and 5-FU plasma concentrations typically rose quickly following dosing, with maximum plasma concentrations achieved in approximately 1 hour. In contrast to tegafur but consistent with the very short plasma half-lives of uracil and 5-FU, plasma concentrations of both the latter drugs decline rapidly after maximum plasma concentrations are achieved.[22] A phase II trial of the above combination in patients with advanced, bidimensionally measurable metastatic colorectal carcinoma demonstrated an overall response rate of 42.2%.[23] These patients had not received prior chemotherapy for metastatic disease. Diarrhea was the major dose-limiting toxicity, with prolonged diarrhea developing at UFT 350 mg/m²/day. The dose was reduced to 300 mg/m²/day. Of importance was the absence of grade 3 or 4 neutropenia, oral mucositis, or hand-foot syndrome. Other phase II studies of UFT plus leucovorin in patients with advanced colorectal cancer have reported response rates and toxicity profiles similar to those reported in the above trial.[24,25]
In two large phase III trials in advanced colorectal cancer, patients are being assigned to receive intravenous 5-FU plus leucovorin or the oral regimen of UFT plus leucovorin. In addition, the National Surgical Adjuvant Breast and Bowel Project (NSABP) has initiated a trial comparing UFT plus oral leucovorin with intravenous weekly 5-FU plus leucovorin as postoperative adjuvant therapy in patients with stage II or III colon carcinoma.

**S-1**

S-1 (BMS-247616) combines tegafur with two 5-FU modulators: 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate at a molar ratio of 1:0.4:1 (tegafur:CDHP:potassium oxonate) (Figure 3).[9,10,26,27] CDHP inhibits 5-FU decomposition and is 200-fold more potent in inhibiting DPD than is uracil. Comparisons between 5-FU levels generated from tegafur plus CDHP and those from tegafur plus uracil indicate significantly higher 5-FU peak levels and AUCs when tegafur is administered with CDHP.[9,26] Potassium oxonate blocks 5-FU phosphorylation by selectively inhibiting it via orotate phosphoribosyltransferase. Since both antitumor activity and gastrointestinal toxicity (ie, diarrhea) are attributed to 5-FU phosphorylation, potassium oxonate selectively inhibits the phosphorylation of 5-FU in normal gastrointestinal tissues while minimizing its inhibition in tumor tissues.

In a phase I study of S-1 reported by the Early Clinical Studies Group of the European Organization for Research and Treatment of Cancer (EORTC), S-1 was administered twice daily for 4 weeks followed by a 1-week rest period. The maximum tolerated dose in this study was 45 mg/m² twice daily for 4 weeks; the dose-limiting-toxicity was diarrhea.[28] Pharmacokinetic studies demonstrated that S-1 effectively inhibited DPD, resulting in cytotoxic 5-FU concentrations. In Japan, phase II trials of S-1 have indicated its impressive activity in advanced gastric cancer, (49% complete and partial response rate), and colorectal cancer (35.5% responses rate), and a mild toxicity profile was reported.[29,30] Myelosuppression was the dose-limiting toxicity reported in Japanese trials. The incidence of gastrointestinal toxic effects in the Japanese trials was low, suggesting the influence of potassium oxonate in reducing diarrhea.[29-33]

**Conclusions**

The agents discussed herein, capecitabine, UFT plus leucovorin, and S-1, contain prodrugs of 5-FU that are converted in vivo to 5-FU to exert antitumor activity. These drugs circumvent the problem of erratic oral absorption of 5-FU by being absorbed as intact molecules (capecitabine and tegafur) and subsequently being converted to 5-FU. Preclinical studies suggest that these agents may produce antitumor activity superior to that produced by intravenous 5-FU by achieving higher intratumoral 5-FU levels, by providing sustained 5-FU exposure, or by biochemically modulating 5-FU. Whether these preclinical rationales translate into improved therapeutic activity in the treatment of advanced colorectal cancer will be determined in phase III trials. Phase III trials are comparing each agent with bolus regimens of 5-FU plus leucovorin with regard to antitumor activity, toxicity, symptom improvement, quality of life, and treatment cost. These agents must demonstrate patient survival that is at least equivalent to that produced by standard intravenous 5-FU-plus-leucovorin regimens in addition to benefits such as greater ease of administration and decreased toxicity.

**References:**


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