Oral Chemotherapy for Colorectal Cancer: An Update

By Sunil Sharma, MD

ABSTRACT

Several new oral chemotherapy drugs are available or under active development for therapy of colorectal cancers. These drugs include fluoropyrimidine analogs, topoisomerase-I inhibitors, and other target-specific agents. Overall, they have the potential to alter the therapy for colorectal cancers in a substantial manner. However, several unique challenges are being encountered, both in the process of drug development and in drug usage by community oncologists. This article summarizes the most relevant data on these oral agents and highlights the issues facing their development and usage.

Oncology Spectrums *2001;2(4):283-286*

INTRODUCTION

Colon cancer remains a serious cause of cancer-related deaths with an estimated 56,700 deaths in 2001.[1] Treatment of colon cancer is multifactorial and complex, and requires expert medical advice. In early stages of the disease, many patients can be cured by surgical excision of the cancer. The cure rates in patients with stage I and II disease vary from 65–90% without additional therapy.[2] In stage III disease, chemotherapy is usually recommended as an adjuvant therapy. The primary treatment for metastatic (stage IV) disease is chemotherapy, although it is palliative.

Recent developments in the treatment of colon cancer are gradually changing the way chemotherapy is administered. Several novel oral drugs are in development, and they are the focus of this article. Oral medications have some obvious advantages. They are self-administered, easier for patients to take, avoid the expense and inconvenience of the parenteral route of administration, and are often used in outpatients. One of the most cogent arguments for development of oral cancer chemotherapy is that this makes most sense for outpatient therapy. The sections that follow examine this argument in more detail.

NOVEL ORAL CHEMOTHERAPY DRUGS FOR COLON CANCER TREATMENT

Capecitabine

An oral prodrug of 5-fluorouracil (5-FU), capecitabine is converted to 5-FU inside the tumor cell by a three-step process. First, after absorption, it is converted to doxifluridine by a two-step process involving interactions with acylamidase isoenzyme A and cytidine deaminase in the liver. Doxifluridine is converted to 5-FU in tissues by thymidine phosphorylase (TP).[3] Because the levels of TP are higher in some tumor tissues than in normal tissues, there may be a theoretical increase in intratumoral levels of 5-FU in tumor tissue vs healthy tissue. This has indeed been shown in biopsy samples from patients who were administered capecitabine.[4]

In a randomized phase II trial of capecitabine in untreated metastatic colon cancer, three schedules were tested.[5] The first used capecitabine at a dose of 1,331 mg/m²/day continuously. The second was intermittent administration with 2,510 mg/m²/day every 2 of 3 weeks. In the third, a combination of 1,657 mg/m²/day of capecitabine with oral leucovorin (LV) (60 mg/day bid) was given on an intermittent schedule. The response rates were similar across the three arms (23–24%). Intermittent administration was the most dose-dense and was recommended for future development.

Two phase III trials of capecitabine in metastatic colorectal cancer (CRC) have been completed.[6,7] The control arm in both trials was the standard Mayo Clinic regimen of 5-FU and LV at 425 mg/m²/day and 20 mg/m²/day, respectively, for 5 days every 4 weeks. The overall results indicated that there was a statistically higher response rate in the capecitabine arm (18.9–24.8% vs 11.6–15%). An independent and a pooled analysis demonstrated no increase in survival for capecitabine vs 5-FU.[3]

In assessing toxicity of capecitabine, the data from the randomized phase II and phase III trials are illuminating. Most patients in the single-agent intermittent arm tolerated treatment well without grade 3 or 4 toxicity. The incidence of hand and foot syndrome (grade 2 and 3) varies from 17.5–30%. Diarrhea (grade 2 and 3) was seen in 15–24% of patients. Other common side effects included nausea and vomiting. Hyperbilirubinemia has also been reported in up to 23% of patients in large studies. This is generally self-limiting if treatment is withheld and patients can be safely retreated with capecitabine.

Most interestingly, dose reductions were required in up to 30–35% of patients who started on 2,500 mg/m²/day of

Dr. Sharma is clinical assistant attending physician in the Gastrointestinal Oncology Service in the Division of Solid Tumor Oncology, Department of Medicine, at Memorial Sloan-Kettering Cancer Center in New York, NY. He is also instructor of medicine in the Department of Medicine at Weill Medical College, Cornell University in Ithaca, New York.

capecitabine.[6,7] Thus, a reasonable approach may be to start a patient at a lower dose (2,000 mg/m²/day) and escalate after tolerance has been demonstrated. This strategy is supported by a retrospective analysis.[8] Recent data have suggested that combination of irinotecan with 5-FU may be the preferred first-line therapy for metastatic colorectal carcinoma. In view of this, capecitabine is often utilized as a second-line treatment regimen (if oxaliplatin is not available) or as a third-line regimen (if oxaliplatin is available) in the United States. No data are available on the efficacy of capecitabine in this setting. In one published study, capecitabine had a low response rate (3.6%) in patients who had failed multiple fluoropyrimidine regimens.[9] Interestingly, 71.4% of patients had stable disease for a median duration of 15 weeks. Similar results were seen in another study from M.D. Anderson Cancer Center.[10]

Currently, a large, international, phase III randomized trial is enrolling patients to compare capecitabine with 5-FU and LV in stage III colon cancer. A combination study of capecitabine and oxaliplatin was reported in patients with solid tumors.[11] A combination of oxaliplatin at a dose of 130 mg/m² with capecitabine at a dose of 2,000 mg/m²/day was tolerable on a 2 of every 3 weeks schedule. Interestingly, no hematologic toxicity was reported, which is distinct from oxaliplatin and 5-FU combinations. The study was small, but five of nine patients had a partial response to this combination.[11]

Capecitabine has also been combined with irinotecan. In a recently published study of this combination as first-line therapy for CRC, dose-limiting toxicities were neutropenia and diarrhea.[12] The recommended dose for phase II trials was capecitabine 2,500 mg/m² on a bid schedule on days 1 through 14 and days 22 through 35 in combination with irinotecan 70 mg/m²/week for 6 weeks. This was followed by 1-week rest in the first cycle and thereafter capecitabine was given as a continuous bid dosing at a total dose of 2,500 mg/m². Four patients with CRC had objective responses.

Capecitabine has also been studied in combination with radiation. In preclinical studies, a combination of capecitabine and radiation therapy was synergistic, probably secondary to upregulation of thymidine phosphorylase by radiation therapy.[13] In a preliminary feasibility trial, a dose of 1,300 mg/m²/day of capecitabine was tolerable on a continuous basis with radiation therapy to the pelvis for 6 weeks in patients with CRC.[14]

UFT

UFT is a combination of uracil and tegafur in a 4:1 molar ratio. Tegafur, available in Japan for a long time, has been extensively studied. It is absorbed intact, is a substrate for the P450 enzyme system, and is converted to 5-FU. Uracil is a substrate for dihydropyrimidine dehydrogenase (DPD), an enzyme that catalyzes 5-FU; thus, the combination of these agents makes it possible to circumvent the normal destruction of 5-FU by the gut DPD.[15,16]

Two phase III trials have been completed in metastatic CRC.[17,18] In a European trial, 380 patients were randomized to receive UFT (300 mg/m²/day) in combination with oral LV (90 mg/m²/day) given for 28 of 35 days, or, in a modified Mayo Clinic 5-FU arm, 5-FU/LV was given for 5 days every 5 weeks instead of every 4 weeks for 2 cycles followed by the 5-week cycles. The overall response rates were low in both arms (11% for UFT/LV, 9% for 5-FU/LV). Neither this nor median survival (12.2 months for UFT/LV, 11.9 months for 5-FU/LV) was statistically different.

In the companion trial, the randomized arms were identical except that the LV dose in the UFT arm varied from 75–90 mg/m²/day and the Mayo Clinic arm was standard. This trial also demonstrated no statistical difference in response rates or overall survival. The side-effect profiles in the UFT/LV arm were significantly different from those in the Mayo Clinic 5-FU arm. There was significantly less febrile neutropenia, nausea, vomiting, hand-foot syndrome, and mucositis in the UFT arm. Liver function abnormalities were seen more often with UFT/LV. Thus it appears that UFT/LV is better tolerated with similar results as 5-FU/LV in patients with metastatic CRC.

The development of UFT/LV is proceeding on several fronts. The NSABP C-06 trial has completed accrual to compare UFT 300 mg/m²/day in combination with LV 90 mg/m²/day for 28 days with 5-FU 500 mg/m²/day and LV 500 mg/m²/day once a week for 6 of 8 weeks for 3 cycles.[19] Preliminary results of other combination trials are now available. In a phase I/II study of the combination of UFT/LV and irinotecan, UFT (250 mg/m²/day) with LV (90 mg/m²/day) was given on days 1 through 14 and irinotecan (250 mg/m²/day) was given on day 1 of a 3-weekly cycle, and appeared to be well tolerated.[20] The overall response rate was about 25%.

In another trial, the combination of oxaliplatin, LV, and UFT was studied as first-line therapy for advanced CRC.[21] Oxaliplatin (85 mg/m² on days 1 and 14), LV (250 mg/m²/day IV on day 1 and then 7.5 mg/m² every 12 hours orally for days 2 through 14), and UFT (300 mg/m²/day as divided doses on days 1 through 14) were tolerable. There was high gastrointestinal toxicity (21% grade 3 or 4 diarrhea, 10% grade 3 or 4 vomiting). Grade 1 neuropathy was observed in 57% of the patients in this trial. The response rate was high (35%).

Other combination trials with oxaliplatin are also under way. In addition, combination trials of UFT with radiation therapy have been reported. In a small feasibility trial, 15 patients with stage II or III rectal cancer were treated with radiation therapy.[22] Concomitant administration of UFT (350 mg/m²/day) in combination with LV (90 mg/m²/day) was tolerable; diarrhea was the major toxicity. A post-operative trial in rectal carcinoma is open and actively accruing patients. Currently, the status of UFT's request for approval in the United States is unclear. The US Food and Drug Administration has asked for clarification on several issues, including the nonstandard Mayo Clinic arm in the flagship trial, and problems with the formulation still have to be resolved.[19]

OTHER ORAL FLUOROPYRIMIDINES

S-1

S-1 is a combination of three different compounds: tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and oxonic acid. While oxonic acid prevents intestinal phosphorylation of 5-FU by pyrimidine-phosphoribosyl-transferase allowing for its absorption, CDHP inhibits activity of DPD and thus prevents degradation of 5-FU. In an early clinical trial carried out by EORTC,[23] main side effects were diarrhea, nausea, fatigue, and anorexia. Plans for further development of this compound in the United States are unclear.

Eniluracil (5-ethynyluracil)

Eniluracil, an inhibitor of DPD, enhances the effects of 5-FU by inactivating its metabolism. It can cause a complete suppression of tumor DPD activity in patients.[24] In combination with oral 5-FU, the major toxicities include mucositis and diarrhea.[25] The response rate in a single-arm phase II trial in combination with 5-FU was 25%.[25] A slightly higher response rate (33%) was seen in combination with LV.[26] However, future development of this compound in the United States for use in patients with CRCs is unclear.

BOF-A2 (emetifur)

BOF-A2 is a combination of 1-ethoxymethyl 5-FU (EM-FU), which releases 5-FU slowly, and 3-cyano-2,6,-dihydropyrimidine (CNDP), which inhibits DPD. It is in development for CRC.[27]

IRINOTECAN

Irinotecan is a topoisomerase-I inhibitor. The intravenous formulation is approved for treatment of metastatic CRC. In a phase I trial, intravenous formulation of irinotecan administered in cranberry juice to patients via the oral route had similar side effects to the intravenous formulation and similar biologic activity [28] Newer capsular formulations are under development and the preliminary results will be presented at the American Society of Clinical Oncology annual meeting this year.

OTHER NOVEL TARGET-SPECIFIC DRUGS

Other novel oral drugs are being developed. These include farnesyl protein transferase inhibitors, cell cycle inhibitors, tyrosine kinase inhibitors, and epidermal growth factor inhibitors. Farnesyl protein transferase inhibitors are designed to inhibit the enzyme farnesyl protein transferase, which is important for processing of the oncogene *ras*. However, these inhibitors probably have other cellular targets as well. Target-specific agents are exciting because they have the potential to minimize toxicity and maximize efficacy by selectively targeting tumor cells. Table 1 lists some of these agents and their current phase of development.

These novel compounds might hold the greatest promise for oral therapy in CRC because they can be given for long periods of time without inconveniencing the patient. Target-specific agents will probably need to be given on a long-term basis because of the need to modulate the target over time. They may be the best candidates for oral chemotherapy. There is also the possibility that at least some of these agents may be synergistic with current chemotherapy agents. Proper design and execution of trials for these compounds remains a particular challenge.

ORAL CHEMOTHERAPY: CHALLENGES FOR PHYSICIANS

Oral chemotherapy is convenient for patients. In surveys, most patients prefer oral therapy to intravenous therapy for a wide variety of reasons, but they are not willing to compromise efficacy simply to take oral therapy.[29] In selecting candidates for oral therapy, the physician and the patient need to understand that the burden of drug administration is being transferred to the patient. Oral therapy affords the opportunity to actively involve patients in their own therapy and assumes that they will be capable of undertaking this complex task. Problems, which can include dose adjustments, dose errors, drug interactions, and inability to follow directions, can be minimized with careful patient selection. Extensive patient education is mandatory, and audiovisual aids such as fact cards, videos, or computer programs that the patient can watch in the physician's office or at home are important. In addition, the physician's staff, especially nursing and pharmacy staff, should monitor the patient by telephone and should check medication logs to assist in this effort.[30]

Although formal compliance assessments in clinical trials have not been reported extensively, in a large phase II trial of UFT/LV in patients with CRC, 99% of patients had a compliance of 80% or greater.[19,20] However, these rates are expected to drop when these drugs are used in the community setting. This decrease in compliance may

TABLE 1. ORAL TARGET SPECIFIC AGENTS IN DEVELOPMENT

Compound name (Manufacturer)	Mechanism of action	Phase of development
SCH 66336 (Schering-Plough)	Farnesyl protein transferase inhibitor	Phase II
R11577 (Janssen)	Farnesyl protein transferase inhibitor	Phase II
OSI 774 (Pfizer)	Epidermal growth factor inhibitor	Phase II
SU 6668 (Pharmacia & Upjohn)	Tyrosine kinase inhibitor	Phase I, II
ZD 1839 (AstraZeneca)	Epidermal growth factor receptor Tyrosine kinase inhibitor	Phase I, possibly Phase II

Sharma S. *Oncology Spectrums.* Vol 2. No 4. 2001.

not be a great concern when these drugs are used for third-line therapy of advanced disease, but it becomes exceedingly important for adjuvant therapy use.

Another serious challenge is the issue of physician reimbursement. Current reimbursement structures do not permit the physician to be reimbursed for most oral drugs as they do for intravenous chemotherapy. This severely limits the incentive to prescribe oral chemotherapy. There is no hard data that the overall cost of chemotherapy is any cheaper when given by oral route. In a preliminary analysis, the money saved by avoiding intravenous administration of chemotherapy may be offset by the higher procurement cost of newer oral drugs.[31] In contrast, a study carried out in Uruguay showed lower administration costs with capecitabine than with 5-FU.[32] This disparity probably results from differing reimbursement patterns and costs of chemotherapy in different countries. A formal pharmacoeconomic analysis comparing oral and intravenous therapy in the United States would be of great interest.

CONCLUSIONS

Several new oral chemotherapy drugs are under development for colon and rectal cancers. As these come on the market, several unique issues, involving patient selection, patient follow-up, and reimbursement to prescribing oncologists, are emerging. While hard data are lacking, there appear to be severe financial disincentives to oncologists to prescribe these therapies. There should be increasing pressure from the oncology community to reform the reimbursement structure for oral chemotherapy.

REFERENCES

1. Greenlee RT, Hill-Harmon B, Taylor M, et al. *Cancer statistics 2001. CA.* 2001;51:15-36.
2. Cohen A, Minsky B, Schilsky R. Colorectal cancer. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer: Principles and Practice of Oncology.* Philadelphia, PA: J.B. Lippincott; 1993:929-977.
3. Marshall JL. Capecitabine in colorectal cancer. *Oncology.* 2001;15(S2):41-47
4. Schuller J, Reigner BG, Durston S, et al. Tumor selectivity of Xeloda in colorectal cancer patients. *Proc Am Soc Clin Oncol.* 1997;16:A797.
5. Findlay M, Van Custem E, Kocha W, et al. A randomized phase II study of Xeloda (capecitabine) in patients with advanced colorectal cancer. *Proc Am Soc Clin Oncol.* 1997;798a.
6. Twelves C, Harper P, Van Custem E, et al. A phase III trial (S014796) of Xeloda in previously untreated advanced/ metastatic colorectal cancer. *Proc Am Soc Clin Oncol.* 1999;18:A1010.
7. Cox JV, Pazdur R, Thibault A, et al. A phase III trial of Xeloda in previously untreated advanced/ metastatic colorectal cancer. *Proc Am Soc Clin Oncol.* 1999;18:A1016.
8. O'Shaughnessy J, Blum J. A retrospective evaluation of the impact of dose reduction in patients treated with Xeloda (capecitabine). *Proc Am Soc Clin Oncol.* 2000;19:A400.
9. Brockmann B, Magacz A, Bierig S, et al. Capecitabine in the treatment of metastatic colorectal cancer. *Ann Oncol.* 2000;11(S4):A239P.
10. Hoff P, Abbruzzese JL, Medgyesy D, et al. A phase II study of Xeloda (capecitabine) in patients with metastatic colorectal cancer demonstrating progression on 5-FU therapy. *Proc Am Soc Clin Oncol.* 2000;19:A993.
11. Evans J, Tabernero J, Cassidy J, et al. Safety profile and preliminary efficacy of capecitabine (Xeloda) in combination with oxaliplatin in patients with advanced or metastatic solid tumors: results from a phase I study. *Ann Oncol.* 2000;11(S4):A222P.
12. Vanhoefer UJ, Mayer S, Achterrath W, et al. Phase I study of capecitabine in combination with a weekly schedule of irinotecan as first line chemotherapy in metastatic colorectal cancer. *Ann Oncol.* 2000;11(S4):A212P.
13. Sawada N, Ishikawa T, Sekiguchi F, et al. X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of capecitabine (Xeloda) in human cancer xenografts. *Clin Cancer Res.* 1999;5:2948-2953.
14. Dunst J, Reese T, Frings S. Phase I study of capecitabine combined with standard radiotherapy in patients with rectal cancer. *Proc Am Soc Clin Oncol.* 2000;19:A995.
15. Ohyama K, Koike D, Odake Y, et al. Antineoplastic effect of UFT therapy (uracil-FT-207 combination therapy) on experimental pancreatic cancer transplanted in the pancreas and subcutaneous region. *Jpn J Cancer Chemotherapy.* 1982;9:2168-2174.
16. Fukui T, Imbayashi N, Nishi M, et al. Clinical study on the enhancement of drug delivery into tumor tissue by using UFT. *Jpn J Cancer Chemotherapy.* 1980;7:2124-2129.
17. Pazdur R, Douillard J-Y, Skillings JR, et al. Multicenter phase III study of 5-fluorouracil (5-FU) or UFT in combination with leucovorin (LV) in patients with metastatic colorectal cancer. *Proc Am Soc Clin Oncol.* 1999;18:A1009.
18. Carmichael J, Popiela T, Raditon D, et al. Randomized comparative study of ORZEL (oral uracil/tegafur [UFT] plus leucovorin [LV] vs parenteral 5-fluorouracil (5-FU) plus LV in patients with metastatic colorectal cancer. *Proc Am Soc Clin Oncol.* 1999:18:A1015.
19. Sun W, Haller D. UFT in the treatment of colorectal and breast cancer. *Oncology.* 2001:15(S2):49-56.
20. Hill M, Mackay H, Cunningham D, et al. Phase I/II study of oral uracil/tegafur (UFT), leucovorin and irinotecan in patients with advanced colorectal cancer. *Ann Oncol.* 2000;11(S4):A193P.
21. Dorta FJ, Feliu J, Vincent J, et al. Phase II clinical trial with the combination of oxaliplatin-UFT-l, leucovorin (OXA-UFT-l, LV) for the first line treatment of advanced colorectal cancer (ACC). Preliminary results (Oncopaz Cooperative group-Spain). *Ann Oncol.* 2000;11(S4):A220P.
22. Hoff PM, Janjan N, Saad ED, et al. Phase I study of preoperative oral uracil and tegafur plus leucovorin and radiation therapy in rectal cancer. *J Clin Oncol.* 2000;18:3529-3534.
23. Vermoken J, Schoffski P, Schellens J, et al. S-1 in colorectal cancer (CRC): interim results of an early phase II study. *Ann Oncol.* 2000;11(S4):A262PD.
24. McLeod HL, Ahmed FY, Johnston SJ, et al. Eniluracil treatment completely inactivates dihydropyrimidine dehydrogenase in colorectal cancers. *Proc Am Soc Clin Oncol.* 1999;18:A772.
25. Mani S, Hochster H, Beck T, et al. multicenter phase ii study to evaluate a 28-day regimen of oral fluorouracil plus eniluracil in the treatment of patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2000;18:2894-2901.
26. Schilsky R, Bukowski R, Burris H, et al. A phase II study of 5-fluorouracil (5-FU) plus GW776 (776C85) with or without leucovorin in patients with metastatic colorectal cancer. *Proc Am Soc Clin Oncol.* 1997;16:A271.
27. Matei S, Hoff PM, Brito R, et al. Phase I trial of oral BOF-A2 plus leucovorin (LV) in advanced colorectal cancer: Antitumor activity in fluorouracil-resistant patients. *Proc Am Soc Clin Oncol.* 1998;18:A882.
28. Drengler RA, Kuhn JG, Schaaf LJ, et al. Phase I and pharmacokinetic trial of oral irinotecan administered daily for 5 days every 3 weeks in patients with solid tumors. *J Clin Oncol.* 1999;17:685-696.
29. Liu G, Franssen E, Fitch MI, et al. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol.* 1997;15:110-115.
30. Hollywood E, Semple D. Nursing strategies for patients on oral chemotherapy. *Oncology* 2001;15(Suppl 2):37-39.
31. Sharma S, Saltz LB. Oral chemotherapeutic agents for colorectal cancer. *Oncologist.* 2000;5:99-107.
32. Aren O, Calveira S, Banchero P, et al. Cost comparison of two treatment regimens for metastatic colorectal cancer. 5-fluorouracil plus leucovorin vs capecitabine. *Ann Oncol.* 2000;11(S4):A243.