Oral Therapy for Colorectal Cancer: How to Choose

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Either alone or in combination with other antineoplastics, fluorouracil (5-FU) has been the mainstay of treatment of gastrointestinal, breast, and head and neck cancers for the past 40 years. Numerous active 5-FU schedules are in

**Introduction**

Colorectal cancer is the fourth most common malignancy diagnosed in the United States and the second most common cause of cancer death. For several decades, fluorouracil (5-FU) stood alone as the only agent with clinical activity against colorectal cancer. Even with the introduction of irinotecan (Camptosar) and oxaliplatin, 5-FU remains a component of standard adjuvant therapy and the initial management of metastatic disease.

Because of its incomplete and erratic oral bioavailability, 5-FU is commonly administered intravenously.[1] However, patients prefer oral rather than intravenous therapy,[2] with oral treatment potentially more convenient and less costly. Thus, methods to effectively deliver fluorinated pyrimidines orally have recently been developed.

Two general approaches have been undertaken. The first involves the use of prodrugs that are absorbed intact in the gastrointestinal tract and are ultimately converted to 5-FU in normal or tumor tissues. Examples of this method of oral administration are capecitabine (Xeloda) and tegafur, a component of UFT and S-1 (Figure 1).

An alternate approach of delivering 5-FU by the oral route is to block its gastrointestinal degradation via coadministration of an inhibitor of dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme in 5-FU catabolism. Inhibitors of DPD in clinical development include eniluracil; uracil, a component of UFT; and 5-chloro-2,4-dihydroxypyridine (CDHP), a component of S-1 (Figure 1).

Preclinical models suggest an improved therapeutic index with administration of oral fluoropyrimidines. This observation has fueled rapid clinical development of these agents over the past 5 years.

**Mechanisms of Action**

Three distinct mechanisms of action of 5-FU have been described.[5] Fluorouracil is converted to fluorodeoxyuridine (FUdR) by thymidine phosphorylase. Fluorodeoxyuridine is then phosphorylated by thymidine kinase to fluorodeoxyuridine monophosphate (FdUMP). Fluorodeoxyuridine monophosphate forms a stable covalent complex with TS in the presence of the reduced folate cofactor, 5,10-methylenetetrahydrofolate. This inhibition of TS prevents the formation of deoxythymidine monophosphate (dTMP) from deoxyuridine monophosphate (dUMP) and thereby decreases the availability of deoxythymidine triphosphate (dTTP) for DNA replication and repair.

In addition to decreasing the availability of dTTP, the inhibition of TS causes an increase in the amount of dUMP available in the cell. Deoxyuridine monophosphate, like FdUMP, can be anabolized to the triphosphate level. Fluorodeoxyuridine triphosphate (FdUTP) and deoxyuridine triphosphate (dUTP) can be incorporated into DNA, contributing to the inhibition of DNA elongation and altering DNA chain stability.

Furthermore, fluorouridine monophosphate (FUMP) is formed from 5-FU by either the sequential...
actions of uridine phosphorylase and uridine kinase, or the direct action of orotate phosphoribosyltransferase (OPRT) in the presence of phosphoribosylpyrophosphate (PRPP).

Subsequently, FUMP is phosphorylated to form fluorouridine diphosphate (FUDP) and then fluorouridine triphosphate (FUTP). The triphosphate is incorporated into nuclear and cytoplasmic RNA, thereby interfering with normal RNA processing and function.

**Biochemical Modulation**

Fluorouracil has been investigated extensively in the treatment of colorectal malignancies. However, response rates to 5-FU alone rarely exceed 20%. Attempts to improve the efficacy of 5-FU without increasing morbidity have included the addition of biochemical modulators and alterations in administration schedules.[6]

The most successful example of biochemical modulation of 5-FU is the addition of reduced folates in the form of leucovorin to stabilize the ternary complex of FdUMP and TS. A meta-analysis of trials comparing 5-FU alone to 5-FU plus leucovorin found an improved response rate in patients with metastatic colorectal carcinoma treated with the combination (11% vs 23%; P < 10^{-7}).[7] However, there was no impact on overall survival; median survival in patients treated with 5-FU alone was 11 months, compared with 11.5 months in those given 5-FU plus leucovorin.

Many administration schedules of 5-FU have been tested. They differ in patterns of toxicity; however, none of these regimens has demonstrated a major survival advantage.

A recent meta-analysis compared bolus 5-FU (with or without leucovorin) to protracted venous infusions of 5-FU in patients with metastatic colorectal cancer.[8] This analysis, which combined six clinical trials involving 1,219 patients, found an overall response rate of 22% in the patients who received continuous-infusion 5-FU, as opposed to a rate of 14% in patients treated with bolus 5-FU. Patterns of toxicity differed, with severe hematologic toxicity more common with bolus treatment, and hand-foot syndrome more common with infusional therapy.[9] However, there was only a minimal difference in median survival (12.1 months with bolus treatment vs 11.3 months with infusional therapy; P = .04).

**Rationale for Developing Oral Agents**

In a survey study of cancer patients,[2] Liu et al found that patients prefer oral rather than intravenous treatment, but are unwilling to sacrifice tumor response for ease of administration. In this study of 103 patients, 89% stated a preference for oral therapy. Reasons for this choice included convenience and fewer problems with venous access. Nevertheless, 70% of survey respondents were unwilling to accept a lower response rate with oral therapy. Thus, although convenience is an important potential advantage, therapeutic equivalence or superiority is required of oral agents.

Daily oral therapy also has the potential to mimic the pharmacology of protracted intravenous infusions of 5-FU, without the cost, complications, and inconvenience of ambulatory infusion pumps. Given some evidence of an improved therapeutic index for protracted infusion schedules in colorectal cancer,[8-11] the recent clinical development of oral fluoropyrimidines has focused on continuous daily schedules.

**New Target for 5-FU Biochemical Modulation: Catabolism**

Traditionally, efforts at biochemical modulation of 5-FU activity have focused on anabolic pathways. The most successful example of this approach is the use of leucovorin to improve the inhibition of TS by FdUMP.

Recently, however, the role of 5-FU catabolism in toxicity and resistance was recognized. This led to the identification of a new target for biochemical modulation, namely, the enzyme DPD. This rate-limiting enzyme in 5-FU catabolism accounts for 5-FU’s serum half-life of approximately 15 minutes.

In patients with a congenital deficiency of DPD, treatment with standard doses of 5-FU results in severe and life-threatening toxicity associated with prolonged half-life and renal excretion.[12]

Intestinal expression of DPD accounts for the poor oral bioavailability of 5-FU. In animal models, the 5-FU catabolite dihydrofluorouracil has been associated with toxicity and tumor resistance.[13,14] Furthermore, DPD levels in human tumor tissue have been correlated with clinical resistance to 5-FU.[15]

These observations led to the development of DPD inhibitors as biochemical modulators of 5-FU in the hope that inhibition of DPD would permit effective oral administration of 5-FU with an improved therapeutic index compared to intravenous treatment.
Eniluracil

Eniluracil (ethynyluracil) is the prototypical DPD inhibitor in clinical use. In preclinical studies, eniluracil completely and rapidly inactivated DPD in vivo. In a human colon tumor xenograft model, the coadministration of eniluracil improved the therapeutic index, compared to other modulators of 5-FU.[16]

Phase I studies documented that 5-FU administered with eniluracil is 100% orally bioavailable, with a plasma half-life of 4.5 hours following single or repeated daily doses.[17] Eniluracil has no direct antitumor activity and is nontoxic when used as a single agent. Furthermore, DPD in peripheral blood mononuclear cells is rapidly and completely inactivated following a single oral dose of eniluracil.[18]

Schedules of oral 5-FU plus eniluracil that have been explored in phase I trials include daily × 5 administration repeated every 28 days[18] and daily × 28 doses repeated at 5-week intervals.[19] The predominant dose-limiting toxicities of these regimens are neutropenia and diarrhea. Because eniluracil results in prolonged exposure to 5-FU, the maximum tolerated dose of 5-FU is markedly reduced when modulated by eniluracil. Urinary excretion becomes the predominant route of elimination.[20] The area under the concentration × time curve (AUC) for 5-FU given at a dose of 25 mg/m²/d orally for 5 days with concomitant eniluracil is comparable to the AUC achieved with a continuous intravenous infusion of 5-FU at a dose of 1,000 mg/m²/d.[17] Ahmed et al[21] recently documented that eniluracil inactivates intratumoral DPD in patients with colorectal cancer, validating an important pharmacodynamic effect.

Clinical Studies in Colorectal Cancer

Several phase II studies of 5-FU administered with eniluracil in advanced colorectal cancer have been completed. Schilsky et al[22] reported preliminary results of a small study in which oral eniluracil was administered at a dose of 20 mg/d on days 1 to 7, with 5-FU at 25 mg/m²/d on days 1 to 5 of each 28-day cycle. An additional cohort was treated with 5-FU, 20 mg/m², plus leucovorin, 50 mg/d. In previously untreated patients, partial responses were noted in 2 (18%) of 11 patients treated with eniluracil and 5-FU and 4 (33%) of 12 patients who received 5-FU, eniluracil, and leucovorin. The most common severe toxicity was granulocytopenia; 13% of patients required hospitalization for neutropenic fever.

Goldberg et al[23] reported a North Central Cancer Treatment Group study in which 44 previously untreated patients with advanced colorectal cancer were given oral eniluracil at a dose of 50 mg/d on days 1 to 7, with 5-FU, 20 mg/m²/d on days 2 to 6. Treatment was repeated every 28 days. A response rate of 18% was reported.

Mani et al[24] enrolled 54 patients with previously untreated metastatic colorectal cancer in a phase II study of oral eniluracil and 5-FU in a 10:1 ratio, twice daily, for 28 consecutive days repeated at 35-day intervals. The dose of 5-FU was 1.00 to 1.15 mg/m² twice daily. A 24% response rate was seen. Grade 3 and 4 toxicities were uncommon in the trials by Goldberg et al and Mani et al.

Preliminary results of a Cancer and Leukemia Group B study of eniluracil, 50 mg on days 1 to 7, 5-FU, 20 mg/m² on days 2 to 6, and leucovorin, 50 mg on days 2 to 6 showed a response rate of 18% in 54 patients.[25] Severe diarrhea and neutropenia were common in this study.

Several phase III trials comparing the daily oral regimen × 28 days to either continuous infusion 5-FU or bolus 5-FU plus leucovorin regimens have been completed or are underway. The results of these studies have not yet been published.

Of note, severe toxicity has been reported in a few patients who received standard doses of intravenous 5-FU shortly after discontinuing treatment with oral eniluracil plus 5-FU. It is likely that these patients had not yet recovered full DPD activity at the time that they began intravenous 5-FU. Thus, it is recommended that after completion of therapy with eniluracil, additional fluoropyrimidine treatment be delayed for at least 8 weeks to allow adequate recovery of DPD activity.

Tegafur

Tegafur (ftorafur, 1-[2-tetrahydrofuryl]-5-fluorouracil) is a furanyl nucleoside analog of 5-FU introduced almost 30 years ago in a search for a fluoropyrimidine with an improved therapeutic index. Tegafur is absorbed intact via the gastrointestinal tract and is then converted to 5-FU in vivo by hepatic microsomal cytochrome P450 enzymes, as well as through soluble enzyme hydrolysis. The widespread use of tegafur was limited initially because of unacceptably high levels of severe gastrointestinal and central nervous system toxicity seen with intensive course schedules, as well as the lack of sustained plasma levels of 5-FU.[26] However, the recent demonstration of improved tolerability when tegafur is administered orally in protracted daily schedules has renewed interest in
this agent. Clinical activity was observed in 5-FU–sensitive malignancies in initial clinical trials.

**UFT**

In an effort to improve the therapeutic index of tegafur, it is currently being developed in a fixed combination with uracil, a competitive inhibitor of DPD. This product is an orally administered fixed combination of uracil and tegafur in a 4:1 molar ratio. Preclinical studies demonstrated that the addition of uracil to tegafur in these concentrations significantly increases the tumor-to-serum and tumor-to-normal tissue 5-FU ratios.[27]

In human tumor xenografts, UFT had antitumor activity superior to equitoxic doses of intravenous 5-FU. Thus, uracil has the potential to prolong 5-FU exposure and improve its therapeutic index. Several UFT administration schedules have been explored in phase I trials. These studies suggested the possibility of saturable tegafur pharmacokinetics, and split daily dosing was recommended.[28-30] The most common dose-limiting toxicities were neutropenia with intensive dosing, and diarrhea with protracted daily schedules. Early phase II studies have shown single-agent UFT activity similar to that expected with intravenous 5-FU.[31-33]

Nakazato et al[34] reported preliminary results of a trial comparing adjuvant UFT (400 mg/d for 2 years) following definitive resection of Dukes’ B and C colon and rectal carcinomas to surgery alone. Disease-free survival rates at 4 years were 76.3% for the UFT-treated group and 63.2% for the control group (P = .0267), although there was no difference in overall survival. These results are intriguing, but interpretation is complicated by the heterogeneity of the study population (colon and rectal cancers; stages B and C).

**UFT Plus Leucovorin**

Recent clinical development of UFT has included coadministration of leucovorin as an additional biochemical modulator (UFT plus leucovorin is being developed under the trade name Orzel). Protracted daily schedules are being pursued in an effort to mimic the pharmacology of infusional 5-FU. Ho et al demonstrated that oral UFT/leucovorin results in higher peak 5-FU concentrations and an AUC similar to that of infusional 5-FU.[35] Phase II studies of oral UFT plus leucovorin administered in three daily doses for 28 consecutive days (repeated at 35 day intervals) showed response rates of 25% to 42% in previously untreated patients with metastatic colorectal cancer.[36-38] However, in patients with colorectal cancer whose disease had progressed on 5-FU-based chemotherapy, no responses were observed.[39,40]

Two large phase III trials have compared treatment with oral UFT/leucovorin to intravenous 5-FU/leucovorin in patients with previously untreated metastatic colorectal cancer. Pazdur et al[41] reported preliminary results of a trial involving 816 patients randomized to receive either UFT (300 mg/m²) and leucovorin (75 or 90 mg/d) in three divided doses for 28 days repeated every 5 weeks or 5-FU (425 mg/m²/d) and leucovorin (20 mg/m²/d) given intravenously for 5 consecutive days every 28 days. The overall response rate was 12% in the UFT/leucovorin arm and 15% in the 5-FU/leucovorin arm (P = .232). No difference in survival was observed. Toxicity profiles differed significantly between the treatments, with more stomatitis and neutropenia in the intravenous arm, and more transient asymptomatic hyperbilirubinemia with UFT/leucovorin. Grade 3-4 diarrhea occurred in 21% of patients treated with UFT and 16% of patients treated with 5-FU (P = NS). No significant incidence of hand-foot syndrome was seen in the patients taking UFT/leucovorin.

In a second phase III trial,[42] Carmichael and colleagues randomized 380 patients to receive either intravenous 5-FU (425 mg/m²/d) and leucovorin (20 mg/m²/d) for 5 days every 35 days or oral UFT (300 mg/m²/d) plus leucovorin (90 mg/d) in three divided doses for 28 days. Overall response rates were 9% for the 5-FU/leucovorin arm and 11% for UFT/leucovorin (P = .593). Median time to progression was 3.3 months with 5-FU/leucovorin vs 3.4 months with UFT/leucovorin (P = .591), and median survival was 11.9 months with 5-FU/leucovorin vs 12.2 months with UFT/leucovorin (P = .682). The toxicity profiles for these regimens were similar to those seen in the trial reported by Pazdur et al.

Taken together, these trials indicate that, compared with a commonly used daily ×5 intravenous 5-FU plus leucovorin regimen, UFT plus leucovorin results in equivalent response rates and survival in previously untreated metastatic colorectal cancer, with a different pattern of toxicity.

The combination of UFT plus leucovorin is also being studied in the adjuvant and neoadjuvant settings. The National Surgical Adjuvant Breast and Bowel Project has completed accrual for a phase III trial (NSABP C-06) of oral UFT/leucovorin vs intravenous weekly 5-FU plus high-dose leucovorin in patients with resected stages II or III colon cancer. The results of this trial have not yet been
Several groups have also reported the preliminary results of trials evaluating the use of UFT plus leucovorin as a radiation sensitizer in the neoadjuvant treatment of rectal cancer.[43,44] This approach appears to be tolerable, with early evidence of antitumor activity.

**S-1**

Another new agent, S-1 (BMS-247616) is a fixed combination of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and oxonic acid in a 1:0.4:1 molar ratio. CDHP is a competitive DPD inhibitor that is 200 times more potent than uracil, while oxonic acid inhibits the enzyme OPRT, preventing 5-FU phosphorylation and the conversion of 5-FU to FUMP. Phosphorylation of 5-FU in the gut is thought to contribute to 5-FU–induced diarrhea.[45] Therefore, oxonic acid may improve the therapeutic index of orally administered tegafur.

Preclinical studies in rodents showed increased bioavailability of 5-FU in animals given S-1, compared to animals given tegafur alone, as well as greater antineoplastic activity.[45,46] In phase I studies with twice-daily dosing for 28 days, the dose-limiting toxicities were diarrhea and neutropenia.[47,48] S-1 exhibits linear pharmacokinetics, with a 5-FU half-life of 2 to 7 hours. An increase in serum uracil concentrations provided indirect evidence of DPD inhibition.[47] Ongoing phase I studies in the United States are exploring several once- and twice-daily administration schedules.

Japanese phase II studies of S-1 have demonstrated antitumor activity against gastric and colon cancers.[49,50] Horikoshi et al.[49] reported responses in 5 (16%) of 30 patients with colorectal cancer treated with 50 to 75 mg of S-1 twice daily × 28 days followed by a 14-day rest. Half of these patients had previously received fluoropyrimidines. Using a similar schedule, Baba et al.[50] administered 40 to 60 mg of S-1 twice daily to 62 previously untreated patients with metastatic colorectal cancer, and reported objective responses in 22 (35.5%). Additional phase II trials of this agent are underway in Europe.

**Capecitabine**

Capecitabine (N4-pentoxycarbonyl-5-α-deoxy-5-fluorocytidine) is an orally administered fluoropyrimidine that is absorbed intact and undergoes a three-step enzymatic conversion to 5-FU (Figure 3). In contrast to the oral agents discussed above, capecitabine does inhibit DPD. In the liver, capecitabine undergoes initial conversion to 5-α-deoxy-5-fluorocytidine by liver carboxylesterase, followed by conversion to 5-α-deoxy-5-fluorouridine by cytidine deaminase in the liver and tumor tissue. The final step is conversion to 5-FU by thymidine phosphorylase (platelet-derived endothelial cell growth factor).

Preliminary studies suggested that colorectal tumors have a high expression of thymidine phosphorylase,[51] and, therefore, the conversion to 5-FU may occur preferentially at the site of disease, potentially improving tumor selectivity. Ishikawa et al.[52] showed a positive correlation between capecitabine activity and the ratio of thymidine phosphorylase to DPD in human cancer xenografts.

In preclinical studies, tumor concentrations of 5-FU were 30 times greater with capecitabine than with 5-FU administered at equitoxic doses.[53] Tumor concentration of 5-FU following oral administration of capecitabine was 100 and 20 times greater than plasma and normal tissue concentrations, respectively.

Preliminary clinical data[54] also demonstrated a higher 5-FU concentration in tumor compared to normal tissue following capecitabine administration. Capecitabine also showed activity against colorectal tumor xenografts that were resistant to 5-FU and UFT.[55,56] Three phase I trials were conducted with different capecitabine administration schedules.[57-59] The pharmacokinetics of capecitabine were similar in each of these studies. Peak plasma levels of capecitabine were observed within 1 hour of dosing, with rapid conversion to its three main metabolites (5-α-deoxy-5-fluorocytidine [DFCR], 5-α-deoxy-5-fluorouridine [DFUR], and 5-FU). As predicted based on preclinical models, plasma levels of 5-FU were quite low. The dose-limiting toxicities in phase I trials were diarrhea, nausea, vomiting, mucositis, leukopenia, and palmar-plantar erythrodysesthesia.

**Clinical Studies in Colorectal Cancer**

The phase I studies led to a randomized, phase II trial in metastatic colorectal cancer.[60] A total of 109 patients with previously untreated metastatic colorectal cancer were randomized to one of three treatment arms derived from the phase I experience: 1,331 mg/m²/d continuously, 2,510 mg/m²/d ×

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14 days repeated every 21 days (intermittent schedule), or the intermittent schedule with the addition of oral leucovorin, 60 mg/d. In each of the arms, the total calculated capecitabine dose was given as two divided doses each day.

Tumor responses were seen in 7 (19%) of 36 patients given continuous therapy, 9 (28%) of 32 treated with intermittent capecitabine alone, and 8 (24%) of 33 who received intermittent capecitabine and leucovorin; median times to progression in the three groups were 17, 30, and 24 weeks, respectively. These results led to the choice of intermittent schedules for further clinical development in colorectal cancer.

Preliminary results of two phase III studies have been reported. Twelves and coworkers[61] compared capecitabine, 2,500 mg/m²/d (in two divided doses) for 14 days every 3 weeks, with 5-FU, 450 mg/m², plus leucovorin, 20 mg/m², administered daily for 5 days every 4 weeks, in 602 patients with metastatic colorectal cancer. In patients who received at least 50% of the planned dose over the first 6 weeks, an investigator-reported response rate of 26.6% was seen with capecitabine, as compared to 17.9% with 5-FU/leucovorin (P = .013). Duration of response, progression-free survival, overall survival, and the rate of serious adverse effects were similar in both arms.

Capecitabine had a higher incidence of hand-foot syndrome (16.2% grade 3) and asymptomatic moderate hyperbilirubinemia (28.3% > 1.5 × normal, 4.7% > 3 × normal), whereas neutropenia (19.7% grade 3-4) and stomatitis (13.4% grade 3-4) were more common among patients receiving 5-FU/leucovorin. Grade 3-4 diarrhea occurred in 10% of patients in both arms of the study. Overall, dose reductions were required in 27% of patients receiving capecitabine and 35% of the patients receiving 5-FU/leucovorin.

Cox et al[62] conducted a similar study comparing capecitabine (2,500 mg/m²/d for 14 days, every 3 weeks) to 5-FU (425 mg/m² with leucovorin, 20 mg/m², on days 1 to 5 every 4 weeks) in 605 patients with advanced/metastatic colorectal cancer. The capecitabine arm had an investigator-reported response rate of 23.2%, while the 5-FU/leucovorin arm had a response rate of 15.5% (P = .02). The duration of response, progression-free survival, and overall survival were similar in the two arms. Again, hand-foot syndrome and asymptomatic hyperbilirubinemia were more common with capecitabine, and neutropenia and mucositis were more frequent with 5-FU/leucovorin.

These initial data suggest that capecitabine results in survival equivalent to 5-FU/leucovorin, with a different toxicity profile. The possibility of superior response rates with capecitabine is encouraging, although an independent review panel was able to confirm this finding only in the study reported by Cox et al.

What's Next?

The development of oral fluoropyrimidines for colorectal cancer continues at a rapid pace. The randomized trials of UFT/leucovorin and capecitabine demonstrate antitumor activity in metastatic disease equivalent to that of intravenous 5-FU plus leucovorin. Based on the clinical outcomes reported in the phase III studies thus far, patient compliance does not appear to be a major obstacle to oral therapy. Completed, ongoing, and planned trials of eniluracil and S-1 may further expand the range of acceptable options for the treatment of metastatic disease.

The results of ongoing randomized trials assessing UFT/leucovorin and capecitabine as adjuvant therapies will help clarify the role of these oral agents in the context of minimal residual disease. As noted above, the use of oral fluoropyrimidines as radiosensitizers in rectal cancer therapy is also being explored. Finally, clinical trials are underway combining oral fluoropyrimidines with irinotecan and oxaliplatin, two other agents with activity in colorectal cancer.

How to Choose?

In the near future, it is likely that medical oncologists worldwide will have several possible fluoropyrimidines available for the treatment of colorectal cancer. To date, the only direct clinical comparisons have been between intravenous 5-FU and oral regimens.

A vast array of new therapeutic agents with novel cellular targets await clinical testing in colorectal cancer. These include agents targeted at growth signaling pathways, angiogenesis inhibitors, and cancer vaccines. For the first time, individuals designing clinical trials must consider a limited patient resource in prioritizing clinical scientific questions. Therefore, it is likely that the various oral agents will not be compared “head to head” a decision that may not be inappropriate. Nevertheless, choices will need to be made in determining the best therapy for an individual patient.

In Table 1, we have attempted to summarize some of the issues that might lead to the choice of a specific fluoropyrimidine for a given patient. Knowledge of tumor phenotype may ultimately play a
role in guiding rational treatment choice. For example, colon cancers that express high TS levels may be likely to show fluoropyrimidine resistance[63]; hence, the use of irinotecan and/or oxaliplatin might be most reasonable in these patients.

In choosing among the various fluoropyrimidines, other issues that may bear on selection include patient compliance (intravenous vs oral), renal function (potent DPD inhibition should be avoided in the presence of renal impairment), tumor DPD expression (which would favor potent DPD inhibition), or tumor thymidine phosphorylase expression (which would favor capecitabine). Clearly, our understanding of the optimal use of the oral fluoropyrimidines is far from complete.

References:


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