Introduction

For over 40 years, the primary therapy for the treatment of colorectal cancer has been intravenous fluorouracil (5-FU), administered as an intravenous bolus, 5-day infusion, or protracted infusion over several weeks.[1] Intravenous 5-FU has also been used in adjuvant regimens for newly diagnosed colorectal cancer, typically as a bolus injection.[2]

As with other therapeutic drug classes, there has been an effort to develop oral dose formulations of drugs used in oncology. The appeal of oral drugs for oncology, as for other disease areas, is for the most part obvious. This includes ease of administration—patients may not need to visit a healthcare facility (eg, a physician’s office or hospital) in order to receive treatment. For the advanced-disease patient, this may allow more meaningful time with family and less time spent in a healthcare facility. For the newly diagnosed patient receiving adjuvant chemotherapy, the availability of oral therapy often permits patients at an early stage of disease to receive treatment while continuing full-time employment. Studies by Liu et al demonstrated that cancer patients preferred oral drugs to their intravenous counterparts as long as they were assured that efficacy was maintained with the oral formulation.[3]

However, several pharmacologic requirements must be met in developing an oral formulation.[4] These include demonstrated stability of the medication in the gastrointestinal tract and ability to be absorbed from the gastrointestinal tract with sufficient bioavailability to assure dosing decisions. Other factors, eg, lack of interaction with other orally administered drugs that the patient may be taking, also are important. Additional considerations can limit enthusiasm for oral drugs, including concern about patients’ mental status that may result in inappropriate dosing, or overdosing in situations when chemotherapy should be stopped because of side effects. Other related issues include patient compliance and the difficulty in adequately assessing how much of, and when, the drug was taken.

In oncology, increasing clinical experience with oral chemotherapy agents has been accumulated[5] and includes oral mercaptopurines, nitrosoureas, hydroxyurea, and methotrexate. Several other new oral chemotherapy agents are currently under investigation. Thus, more orally administered agents for the treatment of cancer are likely to be available in the future.

In particular, five oral fluoropyrimidine drugs have recently entered clinical trials in the United States. These include capecitabine (Xeloda), UFT (uracil and tegafur) or the combination of UFT and leucovorin (Orzel), eniluracil (ethynyluracil), S-1, and BOF A-2. BOF A-2 was associated with severe toxicity, hence clinical studies have been terminated. The other four agents are still under clinical evaluation. The details are described herein.

Capecitabine

Capecitabine is a third-generation fluoropyrimidine drug that was designed to be a selectively activated prodrug that would release 5-FU preferentially within the tumor (Figure 1A).[6] Capecitabine, when administered orally, is absorbed from the gastrointestinal tract into the bloodstream and has excellent bioavailability.[7] This agent is activated by a series of three enzymes in the liver and tumor to eventually release 5-FU within the tumor (Figure 1B). The last of these enzymes—thymidine phosphorylase, localized mainly in the tumor—is responsible for selective
Activation of the metabolite 5'-DFUR to 5-FU.[8]

Capecitabine was approved by the US Food and Drug Administration (FDA) in April 1998 as third-line therapy for patients with paclitaxel (Taxol)- or anthracycline-resistant metastatic breast cancer (or for patients for whom anthracycline was not indicated).[9] In approving this oral fluoropyrimidine, it was noted that there was less severe myelotoxicity and, in particular, less febrile-associated leukopenia than with intravenous infusion of 5-FU. The only toxicity that appeared more prominent with capecitabine was the occurrence of hand/foot syndrome, which was often severe (grade 3). This toxicity, while uncomfortable, is not life threatening and can be managed by withholding therapy for several days or by decreasing the daily dose (typically from the recommended dose of 2,500 to 2,000 mg/m²/d).

Capecitabine has also been evaluated in colorectal cancer. Two large phase III studies compared a capecitabine regimen with a standard Mayo Clinic regimen of 5-FU plus leucovorin. In both trials the capecitabine regimen produced a greater response rate, with survival and time to progression equivalent to that achieved with the Mayo Clinic regimen, but with much less severe toxicity and with potential quality-of-life benefits.[10,11]

At present, capecitabine is not scheduled for a further Oncology Drug Advisory Committee (ODAC) review; approval of this agent for the treatment of advanced colorectal cancer is expected this year. Capecitabine may also have other roles, including acting as a radiosensitizer in rectal cancer and as noted above as adjuvant therapy in colorectal cancer. These studies are currently underway.

**UFT and UFT/Leucovorin**

In the 1970s, tegafur—a prodrug of 5-FU—was synthesized in the hope of having an oral dose form of 5-FU.[12] This drug, however, was associated with many undesirable side effects, and despite being approved in Japan and many other Asian countries, it failed to obtain approval in the United States. In the late 1970s, an attempt was made to improve tegafur by combining it with the naturally occurring pyrimidine uracil, to modulate the metabolism, and in turn the pharmacology, of tegafur. This two-component drug, known as UFT, is composed of uracil and tegafur in a 4:1 ratio (Figure 2).[13]

UFT is currently approved for clinical use in many areas worldwide, including Japan, Asia, South America, and Spain. It is also being evaluated with oral leucovorin as a two-pill combination known as Orzel in an attempt to improve further on the efficacy of the 5-FU formed from UFT.[14]

**Mechanism of Action**

The mechanism of action of UFT and the combination drug UFT plus leucovorin is summarized in Figure 3. Figure 3A demonstrates that the uracil in the UFT combination functions as an "inhibitor" of the important pyrimidine catabolic enzyme dihydropyrimidine dehydrogenase (DPD), which is an important regulatory step in 5-FU metabolism.[15] Uracil is, in fact, a competitive inhibitor of DPD, resulting in 5-FU levels being elevated and sustained for a longer time with the theoretical opportunity for more 5-FU to be anabolized. Because it is a competitive inhibitor, the effect is transient and reverses rapidly once the uracil levels have sufficiently decreased. Figure 3B demonstrates the additional biomodulation produced by leucovorin with UFT plus leucovorin, showing that leucovorin expands the 5,10 methylene tetrahydrofolate pool resulting theoretically in the formation of more ternary complex required for effective inhibition of the synthesis of thymidylate needed for DNA synthesis.

There is extensive experience in the clinical evaluation of UFT worldwide, as it has been approved and used extensively in many countries.[16] UFT plus leucovorin has recently undergone extensive evaluation in clinical trials in phase III studies demonstrating equivalence to the Mayo Clinic regimen of 5-FU plus leucovorin with less severe toxicity.[17,18] In September 1999, the Oncology Drug Advisory Committee of the FDA reviewed the clinical data on UFT plus leucovorin and voted unanimously to approve the drug application. However, the FDA has continued to have concerns about approving either UFT alone or combined with leucovorin. Thus, approvals of both UFT and the...
combination of UFT with leucovorin are currently on hold.

**Radiosensitizer**

It should also be noted that there has been considerable interest in the potential use of UFT as a radiosensitizer for radiotherapy of rectal cancer, as a substitute for continuous-infusion 5-FU. Also, use of UFT plus leucovorin has been evaluated as adjuvant therapy for colorectal cancer in a large multi-institutional study conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP). This study was designed to compare UFT plus leucovorin with a more traditional 5-FU plus leucovorin adjuvant regimen. Accrual has been completed and mature survival data are awaited.

**Eniluracil**

Eniluracil (ethynyluracil, GW776) is another type of DPD inhibitory fluoropyrimidine (DIF) that was synthesized and demonstrated to be a potent inactivator of DPD.[19] The structure of eniluracil, as shown in Figure 4, is similar to that of both uracil and 5-FU. Following interaction with the cofactor NADPH (nicotinamide adenine dinucleotide phosphate) and the enzyme DPD, a covalent bond is formed between eniluracil and DPD that leads to conformational change in the enzyme with complete loss of enzyme activity. Enzyme activity does not return until new enzyme is synthesized.

Because of the interpatient variability in DPD levels, which has been demonstrated to be responsible for much of the variability in the metabolism and pharmacology of 5-FU,[20] it has been suggested that total inactivation of DPD would be desirable. Thus, variability in pharmacokinetics and bioavailability could be decreased, and it may even be possible to use eniluracil to reverse the resistance to fluoropyrimidines due to DPD overexpression in the tumor.[21]

Many of the clinical studies with eniluracil have been completed. Two large phase III studies comparing an eniluracil plus 5-FU oral regimen to a Mayo Clinic regimen of 5-FU plus leucovorin will be presented at the American Society of Clinical Oncology Conference in May 2001. Based on the preliminary results, this drug has been withdrawn by the sponsor (Glaxo Wellcome).

**S-1**

S-1 is made up of three separate component drugs: the 5-FU prodrug tegafur, the DPD inhibitor 5-chloro-2,4-dihydroxypyridine, and the compound potassium oxonate, which has been shown to inhibit orotate phosphoribosyltransferase, the enzyme responsible for the conversion of 5-FU to the nucleotide fluorouridylate monophosphate[22] in the gastrointestinal tract. These components are constituted in a ratio of 1:0.4:1, as shown in Figure 5. It has been suggested that potassium oxonate will be useful in preventing diarrhea, a toxicity that often accompanies fluoropyrimidine drug use.[23]

S-1 has been examined in clinical studies in Japan where it is approved for use in gastric cancer. The Japanese experience suggests that S-1 is associated with decreased gastrointestinal toxicity and diarrhea. Clinical studies of S-1 were recently started in the United States and western Europe. Unfortunately, the dose-limiting toxicity of S-1 in these studies has been diarrhea. It has been suggested that this may reflect a genetic difference in the patient populations, although no objective data supporting this hypothesis are available at present.

**Conclusion**

The expected availability in the near future of an oral fluoropyrimidine approved for the treatment of advanced and potentially newly diagnosed (as adjuvant treatment) colorectal cancer provides motivation for developing oral agents. Since irinotecan (Camptosar, CPT-11) was approved for front-line treatment of patients with advanced colorectal cancer, there has been interest in developing an oral dosage form of camptothecin. Similarly, European studies have demonstrated a role for oxaliplatin (Eloxatin), which has stimulated interest in developing an oral formulation of a platinum analog for potential use in colorectal cancer.
Undoubtedly, as more effective agents for treatment of colorectal cancer are developed, interest in synthesizing oral formulations will increase. This will particularly be true if the oral fluoropyrimidines are approved and demonstrate utility in the clinical practice setting.

References:


Links:
[1] [http://www.diagnosticimaging.com/review-article](http://www.diagnosticimaging.com/review-article)
[2] [http://www.diagnosticimaging.com/authors/robert-b-diasio-md](http://www.diagnosticimaging.com/authors/robert-b-diasio-md)