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Improving Fluorouracil Chemotherapy with Novel Orally Administered Fluoropyrimidines

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Abstract

During the 40 years since the initial synthesis of fluorouracil, there have been many attempts to improve fluoropyrimidine chemotherapy. These have included the utilisation of different schedules of fluorouracil administration, modulation of the metabolism of fluorouracil with other drugs to increase its therapeutic benefit, and the synthesis of prodrugs of fluorouracil that are potentially more effective and less toxic. Of particular interest at present is the clinical evaluation of several new fluoropyrimidine drugs that can be orally administered. These include capecitabine, tegafur/uracil (UFT®), eniluracil (GW-776C85; 5-ethynyluracil), S-1, and emitefur (BOF-A2). The pharmacological principles that have influenced the development of these new drugs are initially presented. This is followed by a review of our current knowledge of the clinical pharmacology of each of these new agents, focusing on antitumour activity and toxicity from studies conducted in the US. Studies of capecitabine, tegafur/uracil, and early studies with eniluracil indicate that these drugs have at least similar activity to protracted fluorouracil infusion but with additional quality-of-life and economic benefits.

Although originally synthesised 40 years ago, the cancer chemotherapy drug fluorouracil continues to be widely used in the treatment of several common human malignancies, including carcinoma of the colon, breast, and skin.[1,2] This drug belongs to the antimetabolite class of chemotherapy agents. It is an analogue of the pyrimidine, uracil, and, as such, is taken up into the cell and metabolised via both anabolic and catabolic pathways similarly to uracil.[2,3] Today, there are a number of fluoropyrimidines that are used as chemotherapy drugs. These include not only fluorouracil and its deoxyribonucleoside, 5-fluoro-2-deoxyuridine (floxuridine; FdUrd), but also several new fluorouracil prodrugs.

The fluoropyrimidine drugs enter the pyrimidine metabolic pathways either directly as the pyrimidine base fluorouracil (possibly formed from fluorouracil prodrug) or as the nucleoside floxuridine. They are then anabolised to nucleotides that interfere with or block normal nucleic acid formation.[2,3] Anabolism has been the major site for biochemical and molecular investigations during the past 4 decades, as it is recognised that these drugs

must first be anabolised before antitumour activity is obtained. Figure 1 illustrates the primary fluoropyrimidine metabolic pathways and demonstrates the 3 major hypothesised sites of action: (i) formation of fluorodeoxyuridine monophosphate (FdUMP), which can complex with thymidylate synthase in the presence of 5,10-methylene tetrahydrofolate to inhibit the formation of thymidylate needed for DNA synthesis; (ii) formation of fluorouridine triphosphate (FUTP), which can be incorporated into newly synthesised RNA, resulting in RNA dysfunction; and (iii) formation of fluorodeoxyuridine triphosphate (FdUTP), which can be incorporated into newly synthesised DNA, resulting in DNA fragmentation.

The fluoropyrimidine drugs also can enter the pyrimidine catabolic pathway as fluorouracil and be converted to metabolites corresponding to the naturally occurring catabolites of uracil (fig. 1). In contrast to anabolism, there has been much less attention focused on catabolism during the past 40 years. Dihydropyrimidine dehydrogenase (dihydrouracil dehydrogenase; dihydrothymine dehydrogenase; uracil reductase; EC 1.3.1.2; DPD) is the initial rate-limiting enzymatic step in the catabolism of not only the naturally occurring pyrimidines uracil and thymine, but also fluorouracil.[4] DPD thus occupies an important position in the overall metabolism of fluorouracil, being responsible for converting more than 85% of clinically administered fluorouracil to the inactive metabolite, 5-FUH_2,[5] in an enzymatic step that is essentially irreversible (fig. 1). While anabolism is clearly essential for the antitumour activity of fluorouracil, catabolism, by indirectly controlling the availability of fluorouracil for anabolism also is a critical determinant of fluorouracil antitumour activity.[2]

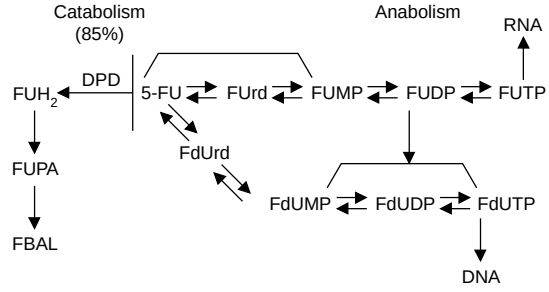

Fig. 1. Metabolic overview illustrating the critical position of dihydropyrimidine dehydrogenase (DPD) in the metabolism of fluorouracil (5-FU) as well as the natural pyrimidines uracil and thymidine. More than 85% of administered fluorouracil is catabolised via DPD. **FBAL** = α-fluoro-β-alamine; **FdUDP** = fluorodeoxyuridine diphosphate; **FdUMP** = fluorodeoxyuridine monophosphate; **FdUrd** = 5-fluoro-2′-deoxyuridine (floxuridine); **FdUTP** = fluorodeoxyuridine triphosphate; **FUDP** = fluorouridine diphosphate; **FUH_2** = dihydrofluorouracil; **FUMP** = fluorouridine monophosphate; **FUPA** = α-fluoro-ureidopropionic acid; **FUrd** = 5-fluorouridine; **FUTP** = fluorouridine triphosphate.

1. Fluorouracil Pharmacotherapy

In general, fluorouracil is relatively well tolerated at standard doses, with typical toxicity occurring in the gastrointestinal mucosa and bone marrow.[1] Fluorouracil is like many other antineoplastic drugs in that it has a relatively narrow therapeutic window, with the effective (antitumour effect) and toxic dose not being very different. Toxicity is likely to increase as the dose (concentration) is escalated. In addition to these toxicities, typically occurring in rapidly growing normal tissues (in S phase), several other toxicities occur that are less well understood, including neurological (cerebellar ataxia and somnolence), cardiovascular, and skin (hand-foot syndrome or palmar-plantar erythrodysesthesia) toxicities.[1] Some of these toxicities have been suggested to be secondary to catabolites of fluorouracil.[6]

During the past 4 decades, many different routes of fluorouracil administration have been explored. By far the most common has been the intravenous route, with drug administered typically as a bolus or as an infusion over hours to days.[1] Another approach made logistically possible by the development of easy-to-place, surgically implanted access sites, together with the use of ambulatory infusion pumps, has been the use of protracted infusions.[7] A number of regional approaches have also been attempted, including administration of fluorouracil by peritoneal belly bath or infusion of the deoxyribosyl nucleoside of fluorouracil (5-fluoro-2′-deoxyuridine; FdUrd) into a blood vessel (e.g.

hepatic artery or portal vein) providing the main blood supply to the tumour site (e.g. liver).[8]

With these different routes of fluorouracil administration (particularly bolus versus infusion), there has been an appreciation of a difference in the frequency of toxicities, especially bone marrow toxicity, which is more likely to occur with short exposures to high fluorouracil concentrations than with more prolonged infusions.

During the past 2 decades, there have also been a number of approaches using biochemical modulation, in which fluorouracil is administered together with another chemotherapeutic or non-chemotherapeutic drug. The goal of these studies is to affect the metabolism of fluorouracil or its ability to act at one of the hypothetical target sites in such a way that the antitumour effectiveness of fluorouracil is increased.[8] Perhaps the most successful and widely used biochemical modulator is folinic acid (leucovorin; 5-formyltetrahydrofolate). When administered together with fluorouracil, folinic acid increases the likelihood of ternary complex formation of 5-FdUMP, 5,10-methylene tetrahydrofolate, and thymidylate synthase, with resultant inhibition of DNA synthesis and, in theory, inhibition of tumour cell division.[9]

In an attempt to improve oral delivery of fluorouracil, a number of different fluoropyrimidine drugs have been synthesised during the past 4 decades. More than 2 decades ago, 2 prodrugs of fluorouracil, 5-fluoro-1-(tetrahydro-2-furyl)-uracil (tegafur; ftorafur) and doxifluridine (5′-DFUR; 5′-deoxyfluorouridine; fortulon) were introduced into the clinic.[8] While the advantage of these drugs was that they could be administered orally, producing a slow release of fluorouracil, there were a number of disturbing toxic effects, including gastrointestinal and central nervous system toxicities. More recently, several additional fluorouracil prodrugs have been synthesised, which have additional pharmacological advantages that tegafur and doxifluridine do not have. These new fluoropyrimidine drugs are listed in table I and are described in detail below.

Table I. Oral fluoropyrimidine drugs

Drug	Chemistry	Development status	Pharmacological characteristics
Capecitabine	Fluoropyrimidine prodrug of 5′-DFUR	FDA approval (1998)	Relatively stable drug; absorbed intact from GI tract 3-step activation; initial metabolism in liver with release of 5′-DFCR or 5′-DFUR Selective conversion of 5′-DFUR to 5-FU in tumour because of potentially higher levels of thymidine phosphorylase
Tegafur/uracil (UFT®)	Uracil and tegafur in a 4 : 1 ratio	Clinical evaluation in US near completion; >1000 patients entered in studies (phase I, II, and III)	Slow release of 5-FU from tegafur, with less degradation of 5-FU because of competition from excess uracil
Eniluracil (5-ethynyluracil; GW-776C85)	Eniluracil is administered with 5-FU in a 10 : 1 ratio	Clinical studies in US underway; currently more than 200 patients evaluable from phase II	Eniluracil rapidly and nearly completely inactivates human DPD, permitting near-complete absorption from GI tract. Theoretical DPD inhibition in tumour
S-1	Tegafur, potassium oxonate, and CDHP in a 1 : 0.4 : 1 molar ratio	Extensively studied in Japan; limited studies in Europe and US	CDHP potent DPD inhibitor Potassium oxonate inhibits 5-FU conversion to FdUMP in GI tract, decreasing diarrhoea
Emitefur (BOF-A2)	1-Ethoxymethyluracil and CNDP in a 1 : 1 ratio	Limited early US studies	Relatively stable drug CNDP potent DPD inhibitor ? optimal dose/schedule

5-FU = fluorouracil; **5′-DFCR** = 5′-fluorodeoxycytidine; **5′-DFUR** = 5-deoxyfluorouridine; **CNDP** = 3-cyano-2,6-dehydroxypyridine; **CDHP** = 5-chloro-2,4-dihydroxypyridine; **DPD** = dihydropyrimidine dehydrogenase; **FdUMP** = fluorodeoxyuridine monophosphate.

1.1 Capecitabine

Capecitabine is the first of the new oral fluoropyrimidine drugs to be approved. This drug is essentially a prodrug of the earlier fluorouracil prodrug, doxifluridine (fig. 2).[10] After oral administration, capecitabine is believed to be absorbed essentially intact in the gastrointestinal tract without metabolism to fluorouracil. This may decrease the likelihood of gastrointestinal toxicity.[11] Once in the liver, capecitabine is initially metabolised by carboxylesterase to 5′-fluorodeoxycytidine (5′-DFCR), which can then be converted in the presence of hepatic or tumour cytidine deaminase to doxifluridine. Within the tumour, doxifluridine is metabolised by thymidine phosphorylase to fluorouracil, which can then be anabolised to the fluorouracil nucleotides responsible for cytotoxicity.[12] Although this is a 3-step activation process, the theoretical advantage is avoidance of fluorouracil in the gastrointestinal tract, lessening the chance of typical fluorouracil-induced gastrointestinal toxicity. At the same time, fluorouracil theoretically can be selectively released in the tumour tissue because of the presence of elevated levels of thymidine phosphorylase in tumour tissue.

After antitumour activity and tolerable toxicity were demonstrated in animal models,[13] capecitabine entered clinical studies in Japan and later in the US. These studies have examined several schedules, including a continuous-dose (twice daily) schedule[14] as well as an intermittent (twice daily × 14 days, with a 7-day rest) schedule.[15] Capecitabine has been used as a single agent as well as in combination with oral calcium folinate (calcium leucovorin). Clinical studies thus far have demonstrated antitumour activity in breast and colorectal cancer that is at least equivalent to that seen with fluorouracil infusion, with the suggestion of durable responses in many of the treated breast cancer patients.[16] Dose-limiting toxicity has included diarrhoea, nausea, and hand-foot syndrome.[17]

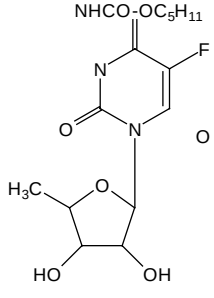

Fig. 2. Structure of capecitabine.

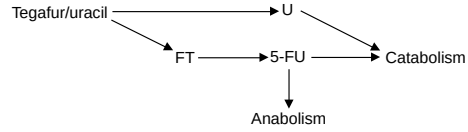

Fig. 3. Composition and mechanism of action of tegafur/uracil (UFT®). An oral formulation of uracil (U) and tegafur (ftorafur; FT) in a 4 **:** 1 molar ratio. **5-FU** = fluorouracil.

1.2 Tegafur/Uracil

Tegafur/uracil (UFT®) will probably be the next oral fluoropyrimidine to be approved in the US. This fluoropyrimidine is a combination of the naturally occurring pyrimidine uracil and the fluoropyrimidine tegafur in a 4 **:** 1 molar ratio (fig. 3).[18] The presence of uracil in excess of fluorouracil ensures competition at the level of the pyrimidine catabolic enzyme DPD, so that the fluorouracil formed from slow tegafur release will not be rapidly degraded but instead will be present over a more prolonged period. Fluorouracil can then enter the anabolic pathway to form active metabolites. Tegafur/uracil is therefore the first of a new class of anticancer agents called DPD inhibitory fluoropyrimidines (DIF).

There is now extensive data from Japan as well as elsewhere[19] demonstrating that orally administered tegafur/uracil has antitumour activity in breast and colon cancer (as well as in several other tumour types). These studies, in which tegafur/uracil was given either as a single agent or

combined with calcium folinate (ORZEL®), demonstrated antitumour activity that was at least equivalent to that of intravenously infused fluorouracil. Furthermore, the toxicity profile has proven to be quite tolerable, with typical fluoropyrimidine toxicities (e.g. diarrhoea and nausea) seen at the maximum tolerated dose. Of note is the virtual absence of other toxicities, such as hand-foot syndrome, neurological toxicity, and cardiotoxicity, which may be secondary to fluorouracil catabolites.[20] Since fluorouracil catabolites are less likely to form from tegafur/uracil, these toxicities are not typically observed.

Other articles in this supplement (see manuscripts by Hoff et al.,[21] Langer,[22] and Ajani & Takiuchi[23]) document the therapeutic efficacy and toxicity profiles of tegafur/uracil in recent clinical studies.

1.3 Eniluracil (GW-776C85)

Since varying DPD levels in both normal and tumour tissues account for the observed variability in fluorouracil pharmacology,[24] direct inhibition of DPD may reduce this variability. Inhibiting DPD in fluorouracil-susceptible host tissue such as gastrointestinal mucosa and bone marrow should reduce patient-to-patient fluorouracil dose variability. Inhibition of DPD in the tumour is also attractive, particularly since many tumours achieve resistance to fluorouracil by developing an increase in DPD activity within the tumour, resulting in increased degradation and thus less anabolism of fluorouracil.[25]

Over the years, there have been many attempts to synthesise effective inhibitors of DPD.[26] Unfortunately, many of these compounds have proven to be very toxic. Recently, a new DPD inhibitor, eniluracil (ethynyluracil; GW-776C85) has been synthesised. This drug, which has a structure similar to those of both uracil and fluorouracil, has been demonstrated to be a potent inactivator of DPD (fig. 4).[27]

Preclinical studies have demonstrated that eniluracil can rapidly and completely inactivate DPD at relatively low doses that produce no obvious toxicity in animals.[28] Subsequently, rodent studies showed that fluorouracil could be administered orally, with a bioavailability of approximately 100%.[29] The effectiveness of fluorouracil administered with eniluracil in inhibition of tumour growth has now been demonstrated in several animal models; evidence of complete tumour regression was observed in models in which only a modest antitumour effect had previously been seen.[6]

Initial phase I clinical studies demonstrated that DPD was rapidly and completely inactivated by eniluracil, with inhibition being maintained for more than 1 day at clinically relevant doses.[30] At the present time, a number of phase II studies are evaluating the effectiveness of the coadministration of fluorouracil and eniluracil in a number of different malignancies. Studies thus far have demonstrated that this regimen appears at least as good

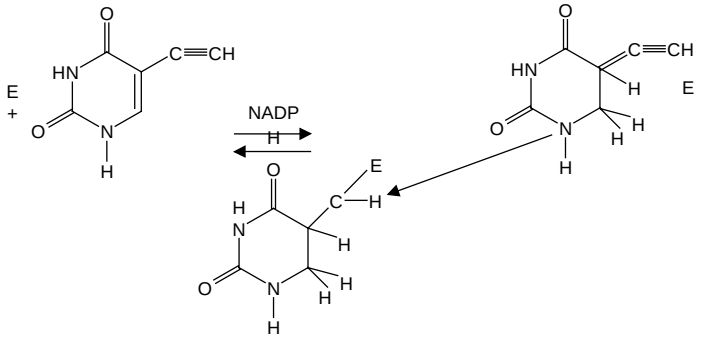

Fig. 4. Structure and mechanism of action of eniluracil (E). **NADP** = nicotinamide-adenine dinucleotide phosphate.

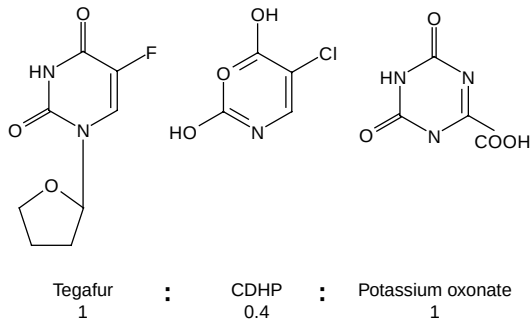

Fig. 5. Structure of S-1. **CDHP** = 5-chloro-2,4-dihydroxypyridine.

as the protracted fluorouracil regimen in colorectal cancer, with efficacy similar to that of fluorouracil in breast cancer.[31] By eliminating fluorouracil degradation, eniluracil may decrease the incidence of bothersome toxicities (such as hand-foot syndrome, cardiotoxicity, and neurotoxicity) thought to be secondary to fluorouracil catabolites.

1.4 S-1

S-1 is a triple-drug combination consisting of the prodrug tegafur, together with a DPD inhibitor 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate in a molar ratio of 1 : 0.4 : 1, respectively (fig. 5).[32] This combination provides the sustained fluorouracil release resulting from the use of the prodrug and the DPD inhibitor. Additionally, potassium oxonate theoretically lessens the chance of the bothersome gastrointestinal toxicity (particularly diarrhoea). Potassium oxonate has been shown in preclinical studies to selectively inhibit fluorouracil phosphorylation by the enzyme orotate phosphoribosyltransferase, particularly in the gastrointestinal tract but not in tumour.[33] Preclinical studies have been encouraging, demonstrating excellent antitumour activity.[34]

Clinical studies thus far have included extensive phase II evaluations in Japan,[35,36] where S-1 has been demonstrated to be quite tolerable. The reported low incidence of diarrhoea suggests that potassium oxalate does afford some relative protection from gastrointestinal side effects. Phase I studies have been undertaken in Europe, with limited evaluation in the US.

1.5 Emitefur (BOF-A2)

Emitefur is a 2-drug combination consisting of the fluorouracil prodrug 1-ethoxymethyl-5-fluorouracil (EM-FU) and the DPD inhibitor 3-cyano-2,6-dihydroxypyridine (CNDP) in a 1 : 1 molar ratio.[37] EM-FU is relatively resistant to degradation and is metabolised to fluorouracil by the liver microsomes.

Preclinical studies have confirmed antitumour activity in several animal models and have demonstrated sustained fluorouracil levels resulting from its release. Clinical studies have been undertaken in Japan and more recently in limited studies in the US. It is somewhat early to comment on the possibility of the clinical effectiveness of this drug combination because of the limited availability of patient data. Studies in the US have demonstrated typical fluorouracil-related toxicities, with some patients experiencing more severe toxicity.[38] The questions of dose, schedule, and accompanying drugs (e.g. calcium folinate) are currently being considered.

2. Economic and Quality-of-Life Factors

It should be emphasised that, in addition to the potential of pharmacological benefits and anti-

tumour efficacy, there are several economic and quality-of-life benefits associated with these new fluoropyrimidines. Most important is that fluorouracil can now be administered by the oral route, resulting in potential cost savings and ease of drug administration. Orally administered capecitabine, tegafur/uracil, eniluracil, S-1, and emitefur provide an alternative to protracted infusion of fluorouracil that does not require surgical placement of a venous access or rental of an ambulatory infusion pump, and avoids the cost of intravenous infusion supplies.

Similarly, this regimen also provides a cost saving compared with fluorouracil bolus regimens, which require frequent office visits, or 4- or 5-day continuous infusions that typically require hospitalisation. Lastly, assuming that the patient receives a regimen of equivalent antitumour efficacy without increased toxicity compared with the more traditional fluorouracil regimens, oral administration of these new fluoropyrimidine agents provides an appealing alternative therapy.

3. Conclusions

During the past several years, at least 5 new third generation fluoropyrimidines have been introduced into the clinic in the US. Unlike the earlier fluoropyrimidines, these drugs can be given orally and, in addition, can theoretically produce higher 'effective' levels of fluorouracil. This latter effect is achieved by taking advantage of selective biochemical steps. Within tumours, thymidine phosphorylase can metabolise capecitabine (or, specifically, its metabolite) to fluorouracil, while inhibition of fluorouracil catabolism at the level of DPD is achieved with the DIFs tegafur/uracil, eniluracil plus fluorouracil, S-1, and emitefur. The use of potassium oxonate with S-1 represents an attempt to control the bothersome gastrointestinal toxicity (diarrhoea) observed with many of these drugs. While it is somewhat early to accurately assess clinical antitumour activity in studies in the US, it is apparent from studies of capecitabine, tegafur/uracil, and early studies with eniluracil that these drugs have activity that is at least similar to that of protracted fluorouracil infusion, and may even have increased activity. While many of the toxicities seen with these drugs are typical of fluoropyrimidines, there are some differences between the 5 drugs. Perhaps most impressive is the relative infrequency of hand-foot syndrome in the presence of DPD inhibition. Lastly, all of the new fluoropyrimidines provide an attractive alternative to protracted fluorouracil infusions. Surgical placement of an intravenous access and the costs of an ambulatory infusion pump are avoided, thereby providing a quality-of-life and economic advantage.

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