Prodrug of 5-FU for cancer therapy

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Abstract

The activity of 5-FU is markedly limited by its rapid degradation into 5-FUH $_2$fluoro-5,6-dihydrouracil) via the action of the cytosolic enzyme DPD (Dihydro pyrimidinedehydrogenase), the first enzyme in the catabolic cycle of 5 -FU. It has been demonstrated that this enzyme deactivates more than 85% of the injected dose of 5-FU. Little drug is thus left for anabolism. This encourages the need of prodrug of 5 F-U.

Key words : Prodrug , DPD, 5-FU , fluoropyrimidine and cancer

1. Introduction

A prodrug is defined as a pharmacologically inactive compound that is converted into an active agent by a metabolic bio transformation. The objective is a chemical modification of the antitumor agent [1] to render it temporarily inactive. The prodrugs of 5-FU [2-3] are characterized by a pyrimidine ring with a fluorine atom in position 5. They differ from 5-FU in a variety of chemical alterations. Their main benefit is that of oral administration. They are designed to be well absorbed intact from the gastrointestinal tract and subsequently enzymatically converted into 5-FU in the liver or within the tumor itself, in order to expose the tumor to 5- FU for a longer time but at lower concentrations than those observed after an i.v. bolus, hence minimizing toxicity. New orally administered fluoropyrimidines thus provide protected 5-FU delivery, which offers advantages that include schedule flexibility and reductions in professional health care resource requirements, administration cost and toxicity related hospitalization. These advantages may reduce the overall cost of treatment. In a study of 103 patients, 89% stated a preference for oral therapy. Reasons for this choice included convenience and fewer problems than with venous access. Nevertheless, 70% of survey respondents were unwilling to accept a lower RR with oral therapy. Thus, although convenience is an important potential advantage, therapeutic equivalence or superiority is required for oral agents.

Table 1. Orally-administrable 5-FU drugs

Drug name	Structure (composition)	Concept	Developer
Tegafar	1-(2-Tetrahydrofuryl)-5-fluorouracil	Prodrug, National	Institute for Organic Syntheses (Latvia)
UFT	FT:Uracil= 1:4 Prodrug	, DPD inhibitor	Osaka University (Japan)
5'-DFUR	5-DFUR 5-Deoxy-5fluorouridine	Prodrug Hoffmann	-La Roche (Switzerland); Nippon Roche Research Center (Japan)
S-1	FT:CDHP:OX,O = 1:0.4:1	DPD inhibitor OPRT inhibitor,	Taiho Pharmaceuticals (Japan)
Capecitabine	N4-Pentyloxycarbonyl-5_deoxy-5fluorocytidine	Prodrug Nippon	Roche Research Center (Japan)

Each agent has been developed according to a specification with a well-defined mechanism for liberation of the active principle. Some are designed to function alone and others require co administration of a modulator. The aim is to mimic the pharmacokinetics of 5-FU administered by continuous i.v. infusion, not only by virtue of their chemical structure, but also by careful choice of dosage.

N'-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine, more commonly called capecitabine (CAP) or Xeloda is a cytotoxic agent that is administered orally and should be activated preferentially in tumors. This carbamate of fluoropyrimidine was synthesized in the 1990s by Japanese researchers as an oral formulation [4-7]designed to circumvent the unacceptable toxicity of 5'd5-FUrd. The main limitation of 5'd5-FUrd derives from its gastrointestinal toxicity, attributed to liberation of 5-FU in the small intestine under the action of thymidine phosphorylase (TP, a tumor-associated angiogenesis factor). CAP was thus designed as a prodrug of 5'd5-FUrd that could not be metabolized by TP in the intestine. Indeed, after oral administration , CAP crosses the gastrointestinal barrier intact and is rapidly and almost completely absorbed; thus, diarrhea should not occur with its use.

2. Mechanism of action

Capecitabine (Fig. 1) is subsequently converted into 5-FU in a three-stage mechanism involving several enzymes. In the first step, it is metabolized into 3-deoxy-3Nuorocytidine (5-dFCR) by hepatic carboxyl esterase. 5-dFCR is then deaminated into 5'd5-FUrd by cytidine deaminase, mainly localized in liver and tumor tissues. Finally, 5'd5-FUrd is transformed into 5-FU under the action of TP, an enzyme [4,5] with higher activity in tumor than in normal tissue . Higher levels of 5FU are thus produced within tumors with minimal exposure of healthy tissue to 5FU. It must be underlined that a high phosphorylase activity is good for activation of CAP (Fig. 2) to 5-FU but bad for activation of 5-FU nucleoside derivatives

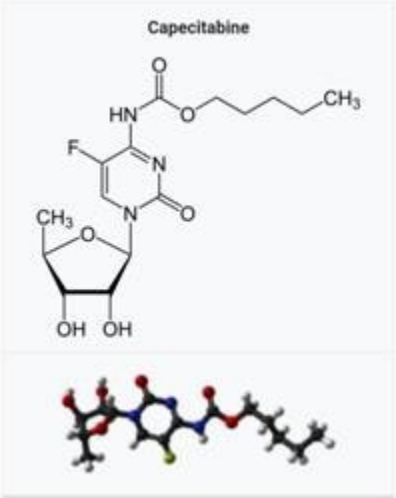

Fig. 1 : Capecitabin

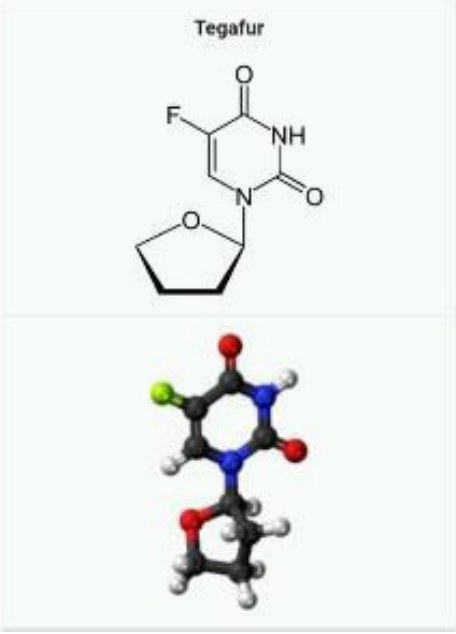

Fig. 2 Tegafur

Up to the nucleotide level. This reaction is in fact bidirectional, but the main direction is toward break down of the nucleosides to the bases.

1-(2-Tetrahydrofuryl)-5-fluorouracil(Tegafur, FT) was developed as a5-FU prodrug . T he benefits of FT including :

1. Excellent absorption from the GI tract
2. Slight conversion to 5-FU in the GI tract.
   The compound 5'd5-FDrd is parentally and orally effective, and its activity was better than that fluorinated pyrimidines available at that time.
   The next generation drugs S-1 (FT , CDHP & OXO) was based on two important things :
   1. 5-chloro-2,44-dihyroxypyrimidine (CDHP) is a DPD inhibitor , and
   2. Potassium oxonate (OXO) is an OPRT (orotatephosphoribosyltransferase) inhibitor.

3. Conclusion

Continuous 5-FU is one of the most widely used cytotoxic drugs. It is usually administered by intravenous bolus or by intravenous infusion. Although the latter route is the most efficient and least toxic, it is costly and inconvenient. Treatment is now increasingly governed by concern for patient quality of life as well as for efficacy. Intravenous infusion requires attendance in a hospital or clinic, which is not without psychological impact on the patient and has a non-negligible risk of complications from catheterization. An oral formulation of 5-FU would be a considerable advance in the treatment of cancer. Unfortunately, due to the activity of DPD, the drug on its own is poorly absorbed and tissue levels are highly variable. The development of new agents that use a specific property of tumors such as CAP, or which inhibit DPD such as UFT and S-1, or act on 5-FU anabolism such as UFT/ LV, has given new impetus to therapeutic strategies [6-12] using fluoropyrimidines. All these compounds have demonstrated therapeutic efficacy. For CAP and UFT/ LV are effective, well-tolerated, and convenient treatments patients with colorectal cancer even if, compared with the classic 5-FULV regimen: they do not improve median survival. The future of these oral drugs rest on documentation of superior or at least equivalent to 5-FU, activity, decreased toxicity, patient convenience, or diminished costs. Oral 5-FU prodrugs will undoubtedly join the list of chemotherapeutic agents, but it is too early to predict whether they will eventually replace 5-FU treatment. Combining oral fluoropyrimidines with drugs such as CPT-11 and oxaliplatin is an exciting prospect .However, the economic advantage that can be gained with oral medications can be lost when combinations employing drugs that need aparenteral administration are prescribed. The advantages of 5-FU prodrugs with respect to conventional treatment regimens will thus need to be proven in future clinical trials.

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