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Unlocking Potential: Capecitabine's Evolution as an Anticancer Wonder Drug

Neha Patil[1], Jaydatta Dhakane[1], Shruti Adhikari[1], Himanshu Solanki[2,*]

Abstract

Capecitabine, a precursor to 5-fluorouracil (5-FU), is Anticancer Drug in treating solid tumors like colorectal, breast, and gastric cancers. Its mechanism involves converting to 5-FU mainly within tumor cells, reducing toxicity while maximizing effectiveness. Besides being effective alone, it is also valuable in combination therapies, showcasing its versatility in cancer treatment. This review explores the transformative journey of capecitabine as a pivotal anticancer drug. Beginning with an introduction to its mechanism of action, drug profile, pharmacokinetics, and pharmacodynamics, the review provides a comprehensive overview of capecitabine's pharmacological characteristics. It further examines the application of capecitabine in various cancers, including colorectal, breast, gastric, and others, highlighting its efficacy and clinical benefits. Moreover, the review delves into capecitabine's integration into combination regimens, such as with oxaliplatin or docetaxel, emphasizing its role in enhancing treatment outcomes and expanding therapeutic options. Through elucidating capecitabine's evolution and versatility, this review underscores its significance as a cornerstone in modern cancer therapy. The continued exploration of its therapeutic potential promises to unlock new avenues for improving cancer treatment and patient outcomes, reaffirming its status as an essential component in the fight against cancer.

Keywords: Capecitabine, 5-fluorouracil, anticancer drug, pharmacokinetics, antineoplastic drugs

INTRODUCTION

Cancer continues to be one of the biggest threats to global public health, affecting millions of lives and demanding ongoing research and development of new treatment approaches. Among the chemotherapy medications, capecitabine has become a mainstay of the therapeutic regimen, providing a strong and adaptable choice for a range of solid tumors. With regard to its pharmacology, clinical efficacy, safety profile, and changing function in the era of precision cancer research, this article attempts to offer a thorough perspective. An important development in the pharmacotherapeutic approach to cancer treatment is capecitabine, an oral prodrug [1]. One of the oldest classes of anticancer medications used by humans is the fluoropyrimidines. 5-fluorouracila fluoropyrimidine drug was first described in 1957 by C. Heidelberger and R. Duschinsky [2]. Fluorouracil (FU) is a type of chemotherapeutic agent which is often used to treat different types solid tumors such as those found in the neck, head, breasts, prostate tissue, the pancreas liver, and parts of the urinary and digestive systems [3].

***Author for Correspondence**
Himanshu Solanki
E-mail: himanshusolanki7ssrcp@gmail.com

[1]Scholar, Department of Pharmaceutics, S.S.R. College of Pharmacy, S.S.R. Campus, Silvassa, Dadra and Nagar Haveli, Daman and Diu, India
[2]Associate Professor, Department of Pharmaceutics, S.S.R. College of Pharmacy, S.S.R. Campus, Silvassa, Dadra and Nagar Haveli, Daman and Diu, India

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Despite 5-Flurouracil's significance for cancer treatment, scientists developed an oral form of the medicine due to its less half-life, the need for a center line, and the continual infusion. In June of 2005, the US FDA approved capecitabine oral prodrug of 5-fluorouracil for use in the adjuvant context for treating stage C colorectal cancer in

Dukes. Comparing capecitabine to conventional 5-Flurouracil, there are several benefits. That is reason for developing it as a prodrug for 5-Flurouracil. Following absorption throughout the digestive system, it undergoes three consecutive enzymatic processes to transform into 5-Flurouracil. Thymidine phosphorylase (TP), the last enzyme in the cycle, is thought to be excessively abundant in tumor tissue, which is thought to improve the agent's tolerance and efficiency through tailored delivery [4]. Capecitabine and 5-FU are thought to have similar efficacies, however they have different toxicity profiles. Both medications cause gastrointestinal adverse effects, with nausea being the most common across comparison treatment groups. When using capecitabine, the frequency of diarrhea is considerably higher [5], especially when paired with irinotecan [6], although the incidence of stomatitis is significantly reduced. Capecitabine is linked to a decreased incidence of neutropenia when compared to intermittent 5-FU; nevertheless, hand-foot syndrome (HFS) is significantly more common [5]. It is well known that neither medication frequently causes cardiac toxicity [7].

With the introduction of precision oncology, a new age of personalized cancer treatment has begun, and treatment selection and prognostication heavily rely on biomarker-driven methodologies. It is a fascinating substrate for biomarker research due to its distinct method of action and clearly defined pharmacokinetic properties. Many genetic polymorphisms in drug-metabolizing enzymes and the production of thymidine phosphorylase are examples of biological markers that have been suggested as potential indicators of the toxicity and response to capecitabine-based treatments [8].

To transport to the site of action in the desired concentration, a number of modified release formulations, including liposomes, enteric coated formulations, micro particles, and matrix systems, have been developed. This article aims to include clinical pharmacy science, mechanisms of action, pharmacokinetics and pharmacodynamics features, clinical effectiveness for colorectal and breast cancers. The impact profile includes proven medication interactions, dosage, and administration. Additionally provided are results from trials that combined it with other chemotherapeutic drugs for new applications.

MECHANISM OF ACTION

It is a prodrug of 5-flurouracil, as a result, it must undergo an enzymatic procedure to transform into 5-flurouracil. Figure 1 displays three metabolic stages involved in the reduction of a drug called cap to its single active component, 5-flurouracil. Capecitabine is transformed to 5'-deoxy-5-fluorocytidine (5'-DFCR) by liver carboxylesterase after absorption via the GI. Cytidine degradation is an enzyme present in high amounts in the liver, plasma, then tumor tissues that transforms 5'-DFCR to 5'DFUR. Lastly, thymine the phosphorylase, which is present at levels from three to ten times larger in various kinds of solid tumors than in typical nearby matter, converts 5'-DFUR into the lively medication, FU [9, 10]. Clinical trials showed decreased systemic toxicity with targeted intra tumoral release of FU due to the enzyme's localization to the liver's tissues and tumor tissue, as opposed to Intravenous FU [11, 12].

Dihydropyrimi-dine dehydrogenase (DPD) catabolizes FU, whereas thymidine phosphorylase anabolisms it. The former is in charge of detoxifying cation and eventual excretion, whereas the anabolic

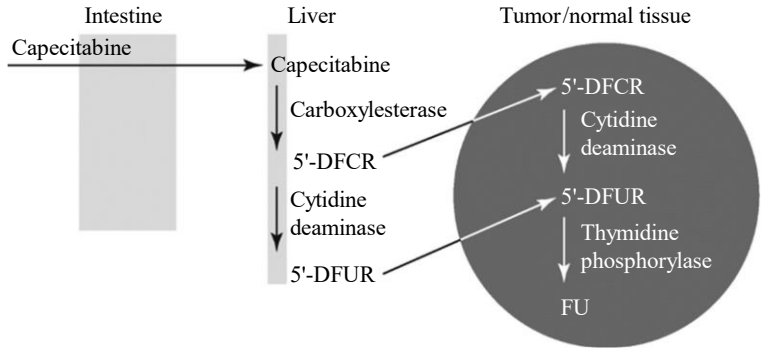


Figure 1. Conversion of capecitabine to its sole active element that is 5-flurouracil.

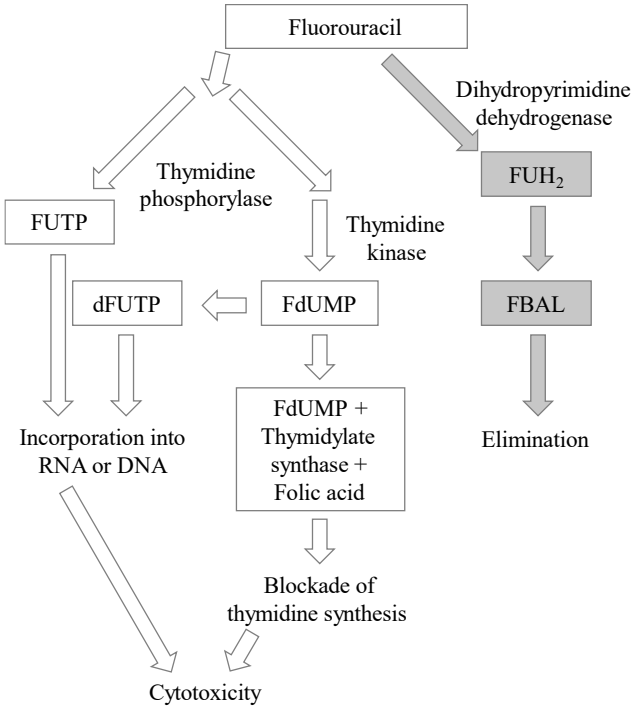


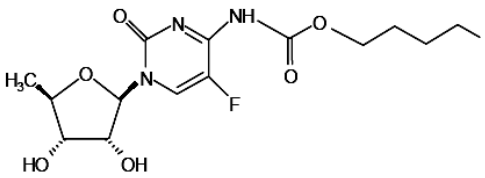
Figure 2. Mechanism of action.

pathway creates the substances with cytotoxic effects. DPD-mediated FU breakdown produces dihydrofluorouracil (FUH2), that transforms into fluoro-p-alanine (FBAL) prior to excretion in the urine which is shown in Figure 2 [13].

Drug Profile

The drug profile of capecitabine describes the description and physicochemical properties. Table 1 describes the drug profile.

Table 1. In Detail profile of capecitabine.

Name	Capecitabine
Structure	
IUPAC Name	pentylN-[1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-methyloxolan-2-yl]-5-fluoro-2-oxopyrimidin-4-yl] carbamate [10].
Molecular Formula	$C_{15}H_{22}FN_3O_6$ [10].
Molecular Weight	359.35 g/mol
Category	Antineoplastic Agents
BCS Class	Class type III
Melting Point	110–121°C
Half life	Elimination half-lives of around 0.75 h. About 30 to 45 min [14].
pKa	1.9 (amide)
Log p	0.4
Physical State	Solid, White crystalline powder
CAS No.	154361-50-9
Solubility	In water, 26 mg/ml at 20°C [14].

PHARMACOKINETICS

Absorption

It is quickly absorbed from the stomach after oral treatment and is subsequently metabolized to its primary metabolites, 5-deoxy-5-fluorocytidine (5-DFCR) and 5-deoxy-5-fluorouridine (5-DFUR). Low 5-FU levels are observed systemically. Concurrent eating considerably lowers systemic exposure to capecitabine. It has been observed in the clinical trials that taking the medication after a meal is beneficial. After consuming food, it takes around 2 h to reach the maximal plasma concentration. Pharmacokinetics in oral form are linear. According to estimates, the bioavailability is about 100% [15, 16].

70% or so are easily absorbed through the GI tract. Capecitabine's AUCs grow similarly between 0.2 and 1.4 times the authorized recommended dose (i.e., 500 and 3,500 mg/m^2/day) for its metabolite 5'-DFCR. Two of capecitabine's metabolites, fluorouracil and 5'-DFUR, demonstrated an AUC rise greater than dose-based. The Cmax and AUC values of fluorouracil varied in over 85% of the individuals. The certified dose of 1,255 mg/m^2 capecitabine, administered twice daily, presented a medium Tmax of unevenly half an hour for the drug and the metabolite a drug called flu, and 2 h for the latter [17, 18].

- *Distribution*: its related metabolites have modest plasma binding percentages, capecitabine 5-dFCR, and 5-dFUR are 54, 10, and 60%, respectively. [19].
- *Metabolism:* After oral administration, capecitabine is largely metabolized in the liver by carboxylesterase to produce 5-DFCR. The enzyme cytidine deaminase, present in the liver and tumor cells turns the metabolite to 5-DFUR, whereas thymine the phosphorylase, an enzyme found in tumor tissue, changes it with the cell to 5-FU. The polymorphically expressed enzyme, dihydropyrimidine dehydrogenase (DPD), catalyzes the deactivation of 5-FU [20].
- *Elimination:* The half-life of capecitabine's elimination ranges from 0.49 of a to 0.89 h. The half-life of the 5-FU metabolite, which ranges from 0.67 as of to 1.15 h, is noticeably longer. Its rapid metabolism by the liver reduces the likelihood of long-term effects and keeps the medication from accumulating in the body. Its metabolism causes a broad spectrum of levels in plasma (27–89%) across individuals, similar to other oral medicines [13, 14].

The drug and its metabolites are eliminated via the kidneys. Patients having serious kidney damage (ClCr<30 ml/min) should not take the drug to avoid an increased risk of adverse effects. Patients with intermediate kidney disease (creatinine clearance (ClCr) of 30–50 ml/min) should take a lower dose of 75% of the initial dose [19].

PHARMACODYNAMICS

As a member of the metabolites class of antineoplastic medications, capecitabine as is a fluoropyrimidine carbamate, which that inhibits DNA synthesis in order to kill cancerous cells [21, 22]. It is an oral systemic prodrug with no pharmacologic effect until enzymes expressed at elevated levels in different tumor types convert it to 5-fluorouracil (5-FU). Capecitabine was developed to alleviate the shortcomings of 5-FU and replicate its infusional pharmacokinetic without the extra complications and issues associated with central veins and infusion pumps [23]. In particular, 5-FU infusion may damage the gastrointestinal tract and lose its efficacy as the gastrointestinal tract has the enzymes needed to convert 5-FU into active metabolites. Specifically, 5-FU can be delivered with capecitabine [24].

CAPECITABINE IN DIFFERENT CANCERS

Breast Cancer

In individuals with metastatic cancer of the breast whose disease progressed during or following anthracycline- and taxane-based treatment, capecitabine has shown strong single-agent efficacy [25]. When treating cancers of the breast, 5-FU is commonly utilized as first-line therapy in conjunction with other cytotoxic medicines. The three 5-FU-based combination regimens that work best are CMF (cyclophosphamide, metho-trexate, and 5-FU), FEC (5-FU, epirubicin, and cyclophosphamide), and FAC (5-FU, doxorubicin, and cyclophosphamide) [26]. Research is still being done to determine whether capecitabine is beneficial in the many combination treatments used for managing cancers of the breast.

Colorectal Cancer

5-FU is a frequently prescribed chemotherapy that has a typical survival time of less than a year and responses vary between 10 and 20%. In adjunctive or advanced/metastatic circumstances, it is also advantageous [27]. For two weeks, capecitabine 1250 mg/m^2 was taken orally twice a day, 30 min after meals, with a one-week break in between. Treatment continued until the 30-week checkup was due, or when clients showed signs of intolerable toxicity or disease progression. The most common side effects requiring dosage reduction were diarrhea and stomatitis in FU-treated individuals and hand-foot syndrome and diarrhea in capecitabine-treated patients [28].

The evidence on metastatic illness is pretty compelling, showing that capecitabine is not less effective than 5-FU when used as therapy or in conjunction with oxaliplatin. This is not the case with combinations containing irinotecan, as studies have not been able to demonstrate that similar outcomes and overlapping toxicity profiles lead to worse acceptance. Capecitabine exhibits promise as a beneficial development in treatment transitioning from infusion-based to oral medication, hence decreasing the amount of time patients must spend obtaining care in a clinic environment [29].

Prostate Cancer

Capecitabine showed anticancer effectiveness during the initial xenograft tests on the PC-3 prostate tumor cell line, resulting in a 77% reduction in multiplication [30]. Furthermore, prostate cancer tissue labeled with immunohistochemistry has revealed the presence of high levels of thymidine phosphorylase in specific types of prostate cancer. To evaluate the effectiveness of single-agent capecitabine, a small subset of patients with metastasis hormone-resistant cancer of the prostate (HRPC) who had advanced after an orchiectomy or medication castration were studied [31].

Ovarian Cancer

In addition, individuals with ovarian cancer require novel therapeutic options. Capecitabine (1,250 mg/m^2 twice daily on days 1–14 of a 21-day phase) has showed promise as a new monotherapy for patients with ovarian cancer who have been treated with taxanes and platinum. Six (32%) of the 19 evaluable strongly pretreated patients (who had received platinum compounds and taxanes) achieved a CA-125 reply, defined by the strict Rustin rules [12], which is defined as a 50 or 75% reduction in CA-125 concentration in order maintained over three or four serial tests, respectively [32]. To find out if capecitabine as may be used as a first-line combination therapy (e.g., with platinum drugs or taxanes) or as an adjuvant to less cytotoxic IV regimes in palliative conditions, study is required.

Pancreatic Cancer

Gemcitabine and/or 5-FU are often employed in the therapy of pancreatic cancer since they are not very sensitive to chemotherapy, either alone or together. However, in patients who have not before undergone therapy, documented response rates are frequently less than 10%, and median survival is typically 3–5 months. TP-activated capecitabine is a prospective therapy in this context since pancreatic cancer is responsive to 5-FU and pancreatic tumor tissue has significantly greater TP activity than surrounding normal tissue. Adults with cancer of the pancreas have also been evaluated for combination treatment with capecitabine and gemcitabine [33].

Renal Cancer

Preclinical investigations on renal cell cultures revealed high TP activity, suggesting that TP-activated capecitabine might be useful in this setting. In a preliminary phase II research, 22 people with advance cancer of the kidney who advanced after or during immunotherapy were given capecitabine (1,250 mg/m^2 twice daily) for 14 days, with a 7-day rest period in between [34]. Renal cell cancer in patients, capecitabine was investigated in the hopes that it may provide therapeutic advantages. A comparable group is presently undergoing evaluation of a docetaxel-capecitabine combination. It is still uncertain whether combination of capecitabine, immunotherapy, and/or chemotherapy is best for renal cell cancer [35].

COMBINATION REGIMENS

1. *Capecitabine and oxaliplatin*: this pair is often utilized in both adjuvant and metastatic situations for the management of colorectal cancer [36].
2. *Capecitabine Plus Docetaxel:* This combo has demonstrated effectiveness as a primary- or second-line treatment for metastatic breast cancer [37].
3. *Capecitabine Plus Trastuzumab:* This HER2-targeted therapy is frequently used in conjunction with capecitabine to treat metastatic breast cancer that is HER2-positive [38].
4. Combining capecitabine with bevacizumab, a vascular endothelium growth factor inhibitor, is a common beneficial choice for metastatic colorectal cancer, especially as first-line therapy [39].
5. *Capecitabine Lapatinib*: This combo is used for advanced or Metastatic HER2-positive cancer of the breast, particularly in patients who have previously been treated with other therapies [40].

CONCLUSION

In this comprehensive review, we have explored the multifaceted evolution of capecitabine as an exceptional anticancer agent. Beginning with an elucidation of its mechanism of action, drug profile, pharmacokinetics, and pharmacodynamics, we gained insight into the intricate workings of this drug. The drug has ability to selectively convert into 5-fluorouracil (5-FU) within tumor cells, exploiting metabolic differences, underscores its targeted approach to cancer treatment. Furthermore, our examination of capecitabine's application across various cancer types reveals its versatility and efficacy. From colorectal to breast and gastric cancers, it has demonstrated significant clinical benefits, contributing to improved patient outcomes and quality of life. Moreover, the discussion on capecitabine's integration into combination regimens highlights its pivotal role in modern cancer therapy. Whether in combination with oxaliplatin, docetaxel, or targeted therapies like trastuzumab, capecitabine enhances treatment efficacy and expands therapeutic options for patients.

As we conclude, capecitabine's journey from discovery to clinical application represents a paradigm shift in anticancer therapeutics. Its evolution signifies a milestone in cancer therapy offers optimism and promise to numerous people impacted by this awful disease. Moving forward, continued research and innovation will further unlock it’s potential, reaffirming its status as an anticancer wonder drug.

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