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Oral Capecitabine vs Intravenous 5-FU in Colorectal Cancer: A Narrative Review

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Abstract:

Background: Colorectal cancer [CRC] is the third most commonly diagnosed cancer and the second most common cause of cancer-related mortality worldwide. 5-fluorouracil [5-FU], administered intravenously, has traditionally been the reference fluoropyrimidine, although the oral prodrug capecitabine is activated by thymidine phosphorylase in tumors. Capecitabine often allows for more convenient administration, eliminates the need for a catheter, and has greater tumor specificity because of the enzymatic conversion to 5-FU.

Objective: The purpose of this paper is to critically analyze and compare at a clinical level the efficacy, safety, pharmacokinetics, mechanism of action, toxicity profiles, and practical considerations of oral capecitabine and intravenous 5-FU in the treatment of CRC, by referencing current trials, meta-analyses, and real-world studies.

Methods: Studies examining the use of capecitabine and 5-FU published from 2015-2025 were reviewed including randomized studies, pooled studies and real-world studies.

Results: Capecitabine demonstrated similar efficacy to 5-FU in adjuvant, metastatic and neoadjuvant scenarios. The IDEA trial showed that three months of CAPOX had similar efficacy to six months for patients with low-risk stage III CRC, although oxaliplatin-induced neuropathy remains an issue. When capecitabine has been used in chemoradiotherapy, it achieved at least equal or better responses compared to 5-FU. Toxicities differed significantly between capecitabine and 5-FU. Capecitabine was more often associated with neutropenia, while 5-FU was more commonly associated with hand-foot syndrome and gastrointestinal- related events.

Conclusion: Capecitabine is a highly efficacious and practical alternative to 5-FU for CRC treatment, and with further advances in pharmacogenetic targeting and combination regimens, gains will continue to be realized in clinical outcomes.

Keywords — Colorectal cancer [CRC], Intravenous 5-fluorouracil [5-FU], Oral Capecitabine, Fluoropyrimidines, CAPOX vs FOLFOX, Disease-free survival [DFS], Patient adherence, Tumor-selective activation, Oral vs intravenous convenience.

I. INTRODUCTION

Among the most frequent malignant tumors of the digestive system, colorectal cancer [CRC] has seen rise in incidence and mortality rates in recent times. Based on the most recent worldwide cancer statistics from 2020 made public by the International Agency for Research on Cancer of the World Health Organization, Ranking third in incidence and second in mortality, the International Agency for Cancer Research [IARC] saw 1.93 million new cases and 940,000 deaths caused by 2,40 CRC worldwide in 2020[1].

Cause of death in North America and Europe with a rate of around 1.2, roughly 600,000 deaths. The survival rate among metastatic CRC [mCRC] patients remains only 10% or less. Therefore, CRC still presents a severe public health issue [2]. Unlike the high occurrence of rectal cancer in the west, in India CRC is not amongst the 10 most frequent malignancies. The age-standardized rates of CRC in India have for men and ladies, been calculated to be 4.2 and 3.2 per 100,000, accordingly [3].

Surgery is still the most often prescribed treatment for CRC; 53.1% of all CRC patients in the United States have undergone surgery. Adjuvant chemotherapy following tumor excision currently regarded as a common treatment for stage III CRC to stop recurrence and extend life. Adjuvant chemotherapy or radiotherapy although chemotherapy has been given to older patients less often than those in other age groups, it improves overall survival and lowers the chance of CRC recurrence[4].

Still central to many chemotherapy regimens, fluoropyrimidines are widely used to treat a broad spectrum of solid malignancies, including those of the head and neck, breast, esophagus, stomach, biliary tract, colorectum, and anus. The fluoropyrimidines used in clinical practice are 5-fluorouracil [5-FU], Capecitabine [Cap],Tegafur,S[tegafur/gimeracil/oteracil], and TAS-102 [trifluridine/tipiracil] [5].

Though intravenous 5-FU is effective, its administration problems and complications lower patients' quality of life. Capecitabine is an oral fluoropyrimidine, developed as a practical substitute with great absorption and tumor selectivity achieved by enzymatic conversion aided by thymidine phosphorylase which is plentiful in tumor tissue. Unlike 5-FU, capecitabine permits simple home-based administration, therefore lowering catheter-related problems including infections and thrombosis. Combined with preoperative chemoradiotherapy, it is harmless, well tolerated, helps to downstage tumors, and raises the likelihood of sphincter-sparing surgery [6].

Oral fluoropyrimidines have evolved as a result of the need for treatments with better efficacy, safety, and patient convenience, yet traditional intravenous 5-FU has been the mainstay of therapy. Capecitabine has been researched extensively among them and has proven non-inferiority to intravenous 5-FU as first-line treatment for metastatic colorectal cancer; there is even evidence suggesting better response rates in some situations. The development from intravenous to oral fluoropyrimidines has therefore broadened treatment options, improved patient quality of life, and preserved the vital relevance of this drug group in current oncology [7].

Emphasis in this narrative review will be on their pharmacology, clinical efficacy, toxicity profiles, patient convenience, and cost-effectiveness, in addition to the present evidence on oral capecitabine and intravenous 5-fluorouracil in colorectal cancer.

II. METHODOLGY

This article is designed as a narrative review, to compile and critically evaluate the novel studies comparing oral capecitabine and intravenous 5-FU [5-FU] in the management of colorectal cancer [CRC]. A narrative is the usual approach for a narrative review, which in turn borrowed common procedures for systematic searches to facilitate fidelity and comprehensiveness.

2.1. Literature search method

With a systematic search approach we reviewed research from the year 2000 on using many electronic databases: PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library covering a wide variety of published research. We created a list of keywords and combined them using Boolean operators. We conducted the following searches using different combinations:

- "colorectal cancer," "colon cancer," OR "rectal cancer"
- "fluoropyrimidine" OR "5-fluorouracil" OR "5- FU"
- "capecitabine"OR "oral fluoropyrimidine"
- "chemotherapy," "adjuvant treatment," "neoadjuvant therapy,"
- "efficacy," "toxicity," "safety," "pharmacology," OR both

2.2. Inclusion and exclusion criteria

Inclusion criteria:

- Original research articles, cohort studies, meta-analyses, systematic reviews, clinical trials [RCTs and non-RCTs], real-world observational publications
- Published studies unpublished covering CRC patients.
- Articles including pharmacology, pharmacokinetics, clinical efficacy, toxicity, survival, quality of life for patients, cost effectiveness.
- Only English language published articles.

Exclusion criteria:

- Letters to the editor, editorials, case reports, and just narrative articles with no current data.
- No freely available full text articles.
- Studies covering other cancers or studies that involve children and have no data on CRC.

I. Results:

3.1. Overview of 5FU and Oral Capecitabine:

A pyrimidine analog called 5-FU needs intracellular activation to create cytotoxic nucleotides. Its oral prodrug capecitabine is intended to mostly produce 5-FU within tissues. Dihydropyrimidine dehydrogenase [DPD] inactivates over 80% of systemically administered 5-FU, hence making DPD the main factor influencing exposure and toxicity through a stepwise enzymatic cascade [8][9] [10].

3.2 Drug Charcteristics and Clinical Features:

Comparative summary of the main pharmacological, clinical, and practical characteristics of oral capecitabine versus intravenous 5-fluorouracil [5-FU] in colorectal cancer is shown in **Table.1**

Table.1 Comparison of Oral Capecitabine vs Intravenous 5-FU in Colorectal Cancer

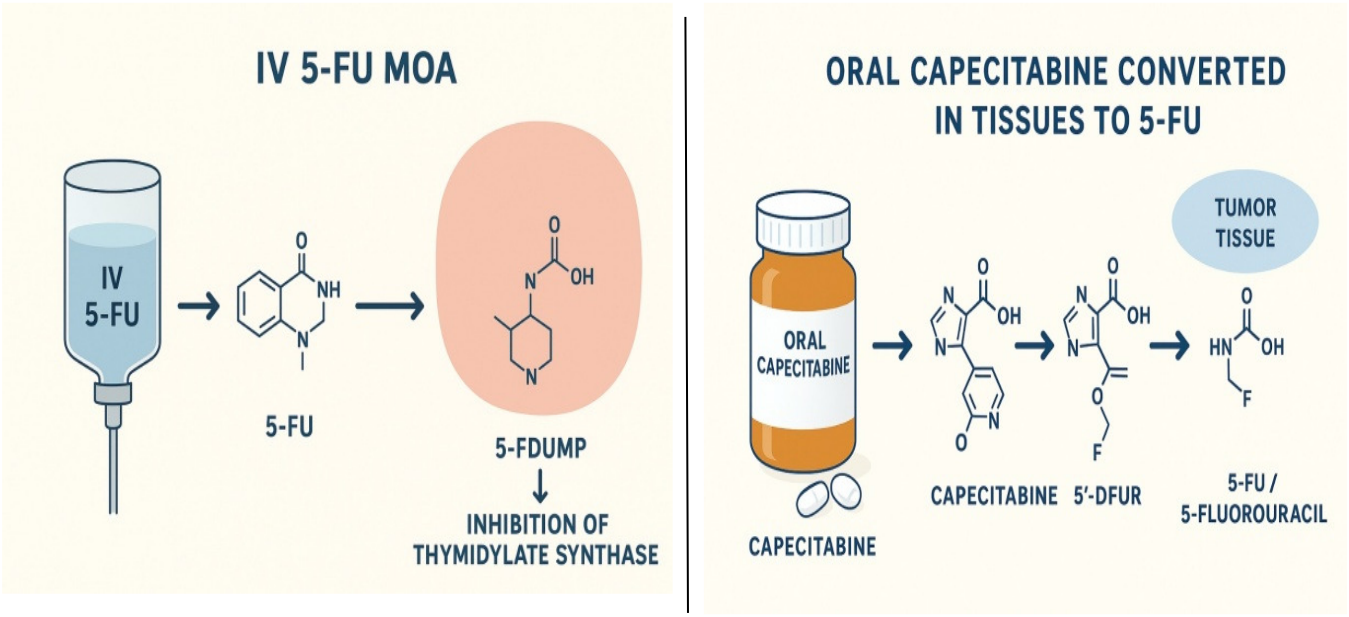
Parameter	Oral Capecitabine	Intravenous 5-FU
Drug nature	Oral prodrug of 5-FU, activated mainly by thymidine phosphorylase in tumor tissue [↑ tumor selectivity].	Direct fluoropyrimidine, requires infusion,systemic exposure depends on DPD metabolism.
Administration	Oral tablets, taken within 30 min after meals, convenient for outpatient use.	IV bolus or continuous infusion, requires central venous access/pump.
Pharmacokinetics	Absorption affected by food [delayed Tmax, reduced Cmax], requires dose adjustment in renal impairment.	Rapid metabolism, 80–85% catabolized by DPD to inactive metabolites, less dependent on renal clearance.
Mechanism of Action	Converted to 5-FU in tumor → inhibition of thymidylate synthase, RNA/DNA misincorporation.	Same final cytotoxic metabolites [FdUMP, FUTP, FdUTP] → inhibition of DNA/RNA synthesis.
Adjuvant Therapy (Stage III CRC)	CAPOX [3 months] non-inferior to 6 months in low-risk stage III (IDEA collaboration).	FOLFOX [6 months] standard, 3 months less effective for high-risk stage III.
Metastatic CRC	Comparable efficacy to infusional 5-FU, supported in multiple RCTs and meta-analyses.	Longstanding standard of care, similar OS/PFS to capecitabine.
Neoadjuvant (LARC)	Higher pCR and R0 resection rates vs 5-FU in CRT (2019 meta-analysis).	Effective in CRT, but slightly lower pCR rates compared to capecitabine.
Toxicity – Hematologic	Less neutropenia/myelosuppression [RR ≈ 0.78 vs 5-FU].	More neutropenia/myelosuppression, especially with bolus dosing.
Toxicity –Non Hematologic	↑ Hand-foot syndrome [40–50%, dose-limiting], diarrhea, stomatitis, renal dose adjustment required.	↑ Mucositis, stomatitis, diarrhea; catheter-related risks [infection, thrombosis].
Neurotoxicity (with oxaliplatin)	Similar cumulative neuropathy as FOLFOX, 3 months therapy reduces long-term neurotoxicity.	Same as capecitabine when combined with oxaliplatin [neuropathy is oxaliplatin-driven].
Special Populations	Dose adjustment in renal impairment; caution in elderly [higher discontinuation], DPD/DPYD testing recommended.	Safer in renal impairment, still requires DPD/DPYD testing to avoid severe toxicity.
Drug interactions	CYP2C9 substrates, interacts with warfarin → ↑ INR/bleeding risk.	Fewer CYP-mediated interactions.
Quality of Life / Convenience	Oral → avoids infusion, catheter care, hospital visits, higher patient preference but adherence monitoring needed.	IV infusion → time-intensive, requires hospital resources, better adherence control.
Cost-effectiveness	Often more cost-effective [less hospital stay, resource use].	Higher healthcare delivery cost [infusion setup, monitoring].

1.3. Mechanism of Action:

5-FU: 5-FU once it enters cells it changes to stable ternary complex with thymidylate synthase [TS] and 5,10-methylene-THF, FdUMP prevents dTMP production and DNA replication "thymineless death"by blocking thymidylate synthase [TS]. Integrated into RNA, FUTP interferes with mRNA splicing and rRNA processing. FdUTP, which can be incorrectly incorporated into DNA.These concurrent paths clarify both tissue-specific toxicities and anticancer action [11] [12]. 5-FU dosage has evolved from bolus intravenous to continuous intravenous infusion plus folinic acid's addition for modifying and enhancing its effects [5]. **[Fig.1]**

Oral Capecitabine: Capecitabine involves three-step activation to 5FU: Capecitabine is converted in the liver by carboxylesterase to 5′-deoxy-5-fluorocytidine, which cytidine deaminase discovered in both healthy tissues and thymidine phosphorylase, an enzyme found in greater levels in tumour tissue and normal liver tissue, is converted from 5′-DFUR to 5FU in the last phase[13]. **[Fig.1]**

Fig1. Diagrammatic representation of oral capecitabine and 5FU mechanism of action



3.4. Pharmacokinetics and administration:

5-FU: Approximately 80–85% of a dose is quickly catabolized to inert dihydrofluorouracil and eventually 5-fluoro-β-alanine [FBAL], thus Hepatic Dihydropyrimidine dehydrogenase[DPD] is rate-limiting [10]. Schedule: Bolus 5-FU promotes RNA incorporation [more myelosuppression], whereas continuous/infusional 5-FU provides more persistent TS inhibition [more HFS/stomatitis]. These schedule-PK/PD variations also help to explain different toxic profiles and clinical results [14].

Oral Capecitabine: Food slows absorption and reduces maximum levels; labels advise taking within 30 minutes after a meal for consistency [15]. Notable interaction: Warfarin/CYP2C9 substrates, clinically significant INR rise/bleeding noted; monitor and change anticoagulant dosage [16].

3.5. Efficacy Evidence:

3.5.1. Metastatic/Advanced and Combination Backbones: Large modern studies spanning oxaliplatin-based backbones reveal no significant loss of efficacy when capecitabine rather than infusional/bolus 5-FU is used as the fluoropyrimidine. The IDEA group [pooled RCTs] established regimen-specific outcomes: 3 months of CAPOX was non-inferior to 6 months for disease free survival [DFS] overall [particularly in low-risk stage III], although this was not verified for FOLFOX, supporting the clinical equivalence of capecitabine as the fluoropyrimidine in effective adjuvant regimens [17] [18].

Generally speaking, real-world and cohort syntheses from 2018 match with IDEA: shorter CAPOX preserves outcomes and lowers neurotoxicity, hence confirming that capecitabine-based treatment maintains effectiveness in regular use. Possibly reflecting selection and dosage variations [nonrandomized], some datasets show mixed overall survival [OS][1][19].

3.5.2. Adjuvant Colon Cancer [Stage III]: Data from six randomized trials [roughly 12,834 originally pooled for the larger project; adjuvant oxaliplatin + fluoropyrimidine arms examined for duration] were pooled under the IDEA collaboration. Regarding disease-free status for individuals getting CAPOX, three months of capecitabine was non-inferior to six months. Thus, this was the main conclusion pertinent to it DFS in the relevant risk groups [especially low-risk T1–3N1]. For DFS in the CAPOX subgroup the hazard ratio [3 versus 6 months] was HR 0.95 [95% CI 0.85–1.06], and 3-year DFS rates were about 75.9%. Supporting usage of shorter CAPOX in many patients, this compares to 74.8% for 3 vs 6 months, respectively. Last pooled/follow-up studies verified that treatment length recommendations should be regimen-specific: in many patients, 3 months of CAPOX is a good standard whereas the same for FOLFOX, uniform recommendation is not possible [17]. The conventional adjuvant treatment for stage III colorectal cancer [CRC]: has long been intravenous 5-FU/leucovorin [LV], which lowers relapse risk relative to surgery only and lowers mortality by around 22%. Patients, nevertheless, sometimes favor oral choices. With the same DFS and OS in older patients, capecitabine, an oral fluoropyrimidine that selectively provides 5-FU to tumors, has demonstrated comparable effectiveness and tolerability to 5-FU/LV. Moreover, adding oxaliplatin to capecitabine has shown to be as safe and effective as 5-FU/LV-based treatments in stage II/III CRC [20].

3.5.3. Neoadjuvant chemoradiotherapy for locally advanced rectal cancer [LARC]:

Higher pathologic complete response [pCR] and greater R0 resection rates with capecitabine were reported in a 2019 meta-analysis of 10 studies [n = 2,916 LARC patients] comparing capecitabine-based CRT versus 5-FU-based CRT: With a 95% confidence interval of 1.10–1.63, pCR OR = 1.34, statistically significant increase in pCR. Capecitabine was also favored in R0 resection OR = 1.92 [95% CI 1.10–3.36]. With capecitabine in the CRT environment, these combined findings point toward at least non-inferior and possibly superior local tumor response [21].

3.6. Safety and toxicity:

Several reviews and observational studies show markedly more Hand and Foot Syndrome [HFS] with capecitabine than with infusional 5-FU. A contemporary meta-analysis/systematic review quantified usual HFS with capecitabine, given that HFS incidence is frequently greater than 40–50% Pooled studies from 2015 indicate fewer neutropenia rates with capecitabine than with IV 5-FU treatments. A recent meta-analysis [systematic review of RCTs] revealed a Capecitabine helps to reduce neutropenia risk: RR ≈ 0.78 [95% CI 0.62–0.98], or roughly 22% relative reduction. This fits trial findings indicating that intravenous 5-FU regimens cause greater myelosuppression than oral or continuous infusion [23].

Modern IDEA pooled studies and final papers stress that when oxaliplatin is used with either CAPOX, oxaliplatin cumulative neurotoxicity is Both medicines are gastrointestinal toxicants, particularly in combination therapies and in patients with dihydropyrimidine dehydrogenase [DPD] deficiency or renal impairment, capecitabine can cause stomatitis and diarrhea. Diarrhea and mucositis are also possible side effects of 5-FU bolus. Although rates of grade ≥3 diarrhea are similar throughout regimens, occurrence rates change according to schedule since capecitabine is given to outpatient, close monitoring is required [21].

3.7. Special Populations

- **Genetic implications**: It is recommended to perform DPD/DPYD testing before starting any fluoropyrimidine (capecitabine or 5-FU). On April 2020, regulatory bodies [EMA] recommended both FDA and DPD routine pre-treatment testing. Safety advisories, as well as guideline groups stressed testing/assessment to decrease serious toxicity. When attainable, either genotyping for clinically relevant DPYD variants or phenotyping [plasma uraci] can be utilised, with dose reductions or substituting drug options for those patients with deficient levels. Implementation of testing significantly improves therapeutic safety [25].
- **Renal Insufficiency**: There have been many reported drug interactions of capecitabine [and 5- FU] and warfarin, frequently associated with significant INR elevations and bleeding in a number of case studies and reviews [2015–2021] requiring nearly continuous INR monitoring and evaluation of different anticoagulation options. General advice has been to do frequent INRs or avoid coprescribing when reasonable [26].
- **Old Age**: Although, in some instances, frail patients only require monotherapy, elderly patients with stage III CRC may derive benefit from 5-FU/LV or capecitabine without added toxicity, and novel targeted therapies are emerging but require continued investigation [27]. While older patients are more capable of tolerating oral capecitabine, they are at greater risk of adverse events. Consider comorbidities, renal function, cognitive/adherence and functional status. Also consider starting at lower doses or increased monitoring. Actual-world studies advocate for caution in using capecitabine

across all grades, and grade ≥3 HFS in a smaller but clinically relevant minority, dose reductions or treatment interruptions follow. The one most typical toxicity driving capecitabine dosage adjustments is HFS [22].

the major dose-limiting toxicity. FOLFOX [infusional 5-FU + oxaliplatin] or[capecitabine + oxaliplatin] should be noted: three months of oxaliplatin-containing therapy versus six months greatly lowers chronic neuropathy:Example: In pooled analyses, grade 2 neurotoxicity frequency was 14% [3 months] vs 36% [6 months] [P < 0.001], this toxicity difference is independent of whether Though it is a significant safety issue when using CAPOX, the fluoropyrimidine backbone was capecitabine or infusional 5-FU[18][24].

II. Discussion

4.1. Efficacy of Capecitabine vs. 5-FU:

Designed as an oral prodrug of 5-FU, capecitabine has tumor-selective activation via thymidine phosphorylase. Its non-inferiority vs 5-FU has been demonstrated by several studies and meta-analysis. For stage III CRC, the IDEA cooperation found CAPOX (capecitabine + oxaliplatin) to be comparable to FOLFOX [infusional 5-FU + oxaliplatin], particularly in patients with lower-risk disease [29]. Phase III research confirmed comparable general survival and progression-free survival in metastatic CRC [30].

Some studies, however, found that continuous infusion 5-FU combined with radiotherapy in rectal cancer offered somewhat improved local control, thereby raising doubt if capecitabine is always comparable [31].

4.2. Toxicity and Safety Considerations:

The toxicity profiles of the two drugs differ. While 5-FU more frequently causes myelosuppression and neutropenia, capecitabine is more closely associated with hand-foot syndrome[HFS]. A large pooled analysis indicated that 50% of patients receiving capecitabine would experience HFS [32)]. In contrast, 5-FU requires central venous access and brings the risks of insertion or catheter-related infections [33].

Still, the information remains contradictory. Some studies report that capecitabine can cause higher rates of mucositis and severe diarrhea, leading to treatment interruptions, than 5-FU [34]. Both agents pose a lethal risk in patients with DPD deficiency. Accordingly, guidelines now recommend DPYD genotyping before beginning treatment [35].

4.3 .Practical Aspects and Future Directions

From a patient's point of view, oral capecitabine is more practical and lowers hospital visits, which is backed by better patient satisfaction scores. Still, this advantage is balanced by compliance issues, especially in elderly or socially isolated patients [36]. While 5-FU is safer in this subgroup, renal dysfunction also makes capecitabine dosage more difficult.

Looking Ahead, further safety might be enhanced by combining DPYD genotyping with perhaps therapeutic drug monitoring. With encouraging first results, capecitabine is also being investigated in conjunction with immunotherapy in MSI-H cancers [37]. Other new oral fluoropyrimidines like trifluridine/tipiracil and S-1 widen treatment choices. Digital adherence and toxicity monitoring tools could help daily usage of oral chemotherapy be more secure.

III. Conclusion:

In colorectal cancer, capecitabine provides oral administration substitute for infusional 5-FU that doesn't sacrifice effectiveness. Although both treatments have comparable survival results, their toxicity profiles vary, therefore patients have to be chosen carefully. Future research including DPYD genotyping, dose optimization, and integration with developing treatments will help clarify the safe and effective use of fluoropyrimidines in daily practice.

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