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Genomic Biomarkers and Clinical Perspectives of Fluoropyrimidines in Cancer Treatment: A Literature Review

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ABSTRACT
Fluoropyrimidines, such as 5-fluorouracil (5-FU), are vital chemotherapy agents against gastric, colorectal, and breast cancer. Despite their efficacy, response and toxicity vary greatly between patients, prompting the search for genomic biomarkers to personalize treatment. In gastric cancer, combinations with fluoropyrimidines and oxaliplatin improve survival, while in colorectal cancer, regimens with 5-FU, oxaliplatin, and irinotecan achieve a 3-year survival rate of 86%, albeit with considerable toxicity. In breast cancer, capecitabine is effective in anthracycline-resistant cases but requires careful risk-benefit assessment. The metabolism of 5-FU is key to understanding these variations. The enzyme dihydropyrimidine dehydrogenase (DPD), encoded by DPYD gene, catabolizes 5-FU. Genetic variants such as DPYD2A (c.1905+1G>A) and c.2846A>T are associated with DPD deficiency, increasing the risk of severe toxicity and mortality. Detection of these variants or elevated blood uracil levels (uracilemia >16 ng/mL) allows for dose adjustments or treatment contraindications. Thymidylate synthase (TS), the target of 5-FU, also influences resistance. Variants in its regulatory region (2R/3R) modulate its expression, affecting efficacy in colorectal and gastric cancer. Other biomarkers include variants in MTHFR, which impact folate availability, and the expression of orotate phosphoribosyltransferase (OPRT) and transporters such as ABCC5. Pharmacogenomics is essential to optimize the safety and efficacy of fluoropyrimidines. Prior genetic screening for critical variants, dose adjustments, and plasma monitoring are recommended. Validation and standardization of these biomarkers across diverse populations is crucial for advancing precision oncology that improves survival and reduces toxicity.

Keywords: *Fluoropyrimidines, cancer, dihydropyrimidine dehydrogenase, gene variant, toxicity*

INTRODUCTION

Fluoropyrimidines (capecitabine, floxuridine, tegafur, and fluorouracil) are a group of antineoplastic drugs that replace thymine in nucleic acids, particularly in DNA, by forming adenine-uracil base pairs. The first to be described was 5-fluorouracil (5-FU), which demonstrated anticancer activity 60 years ago, with adequate incorporation into rat hepatomas, generating cytotoxicity against the tumor (Lam et al., 2016). The response obtained with 5-FU led to structural modifications in the molecule that enabled oral administration of chemotherapy. This led to a reduction in administration times and improved absorption through the gastrointestinal mucosa, maintaining a response equal to that initially seen with 5-FU; this is explained by the capacity for biotransformation in the liver or in the patient's tumor cells (Lam et al., 2016; Vodenkova et al., 2020).

With the progress in cancer research and its response to anticancer agents, a great diversity in response has been detected. An example is gastric cancer, in which a great diversity in the disease has been found, which has allowed individuals with this diagnosis to show a wide variety of responses despite being treated identically (Tan et al., 2011). Since there has been increased interest in research on variability and its influence on the response to the treatments used, evidence has been found of the association between certain variants in genes responsible for metabolism and response to chemotherapeutic agents and the incidence of serious adverse events in patients receiving treatment at the systemic level (Ezzeldin & Diasio, 2004).

Progress in the identification of potential biomarkers involved in drug response has established some foundations for precision medicine in cancer treatment. The goal is to define the correct drug doses for the right patient at the right time, based on the genetic profiles of the cancer and the mutational signatures associated with the individual genotype (Low et al., 2018). This has been achieved through the analysis and storage of a large amount of genome data, where clinically significant variants are identified to implement treatment proposals for these types of pathologies, whether in the form of single nucleotide variants (SNV) or structural variations such as copy number (CNV), indels, inversions, and changes in expression profiles at the genomic level in response to treatments. Pharmacogenomics is a fundamental research tool in the search for genetic determinants and biomarkers of response to chemotherapy, with the projection of finding its application in the clinical field in this new paradigm of cancer treatment (Koch, 2004). In this review, we aimed to locate and select relevant published studies on the pharmacogenomics of cancer treatment with fluoropyrimidines, critically appraise them, and extract and synthesize the findings.

MATERIALS AND METHODS

A rapid descriptive systematic review was conducted in accordance with the recommendations of the practical guide issued by the World Health Organization (WHO) (Page et al., 2022) and the recommendations issued by the PRISMA protocol for rapid reviews (Kelly et al., 2016). The formulation of the systematic review question and the selection of MeSH terms used during the database search were performed using the PICO methodology adjusted for diagnostic tests recommended by the PRISMA-DATA Statement.

The search was restricted to original articles reporting the following MeSH terms in different combinations: fluoropyrimidine, cancer, dihydropyrimidine dehydrogenase, gene variant, and toxicity. The search was conducted in the PubMed, Scielo, Cochrane, and Scopus databases. The English and Spanish-language articles published between 2013 and 2024 (or earlier if the publication warranted it) were the only ones included in the search.

An initial filtering of the articles found was performed by title and abstract, and then the articles were filtered according to the following exclusion criteria: systematic reviews, meta-analyses, opinions,

comments, and letters to the editor; studies with incomplete data or lack of detailed information; duplicate studies; or studies that share the same dataset and results. The results were synthesized in a narrative format, presenting the main findings for each study.

RESULTS

CURRENT USE OF FLUOROPYRIMIDINES IN ONCOLOGY

GASTRIC CANCER (GI)

Gastric cancer represents a significant public health challenge due to its high morbidity and mortality and complex therapeutic management. Although radical surgery remains the standard curative treatment in localized stages, randomized clinical trials have redefined the role of perioperative and adjuvant chemotherapy. Key trials such as CLASSIC, MAGIC, INT0116, FNLCC/FFCD, and ACT-GC demonstrate that regimens based on capecitabine (a prodrug of 5-FU) and oxaliplatin improve overall survival (OS) and progression-free survival (PFS) compared with surgery alone, consolidating their inclusion in international protocols. This evidence supports the recommendations of the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines, which prioritize these regimens in stages II-III (Kang & Cho, 2019). In advanced stages (IIIB and IV), which constitute the majority of diagnoses, adjuvant combination chemotherapy has demonstrated superiority over surgery alone. Meta-analyses and studies such as those referenced (Cervantes et al., 2013; Sano, 2008) confirm that adjuvant chemotherapy increases OS by 15–20% and preserves quality of life, in contrast to conventional palliative management. This benefit is attributed to the reduction of micrometastases and systemic disease control. Regarding therapeutic regimens, 5-fluorouracil (5-FU) and cisplatin remain first-line agents, both as monotherapy and in combination with anthracyclines (e.g., ECF regimen). Phase III studies report a 5-year overall survival rate of 36% with these protocols in neoadjuvant settings, particularly in diffuse and intestinal histological subtypes (Matuschek et al., 2011). However, tumor heterogeneity and population variations have led to regional adaptations of the regimens, supported by pharmacogenomics and pragmatic trials.

COLORECTAL CANCER (CRC)

Colorectal cancer (CRC) is one of the most prevalent neoplasias worldwide, with an estimated annual incidence of 1 to 2 million new cases. Approximately 70% of cases are sporadic, associated with somatic mutations in key genes such as APC (Wnt pathway regulator), KRAS (linked to cell proliferation), TP53 (tumor suppressor), and DCC (involved in apoptosis) (Mármol et al., 2017). In the remaining 30%, hereditary syndromes stand out: familial adenomatous polyposis (FAP) caused by germline mutations in APC. Lynch syndrome (HNPCC): characterized by mutations in DNA repair genes (MSH2, MLH1, MSH6, PMS1, PMS2), which generate microsatellite instability (Mármol et al., 2017).

In the therapeutic setting, chemotherapy for CRC is based on fluoropyrimidines (5-FU, capecitabine), combined with agents such as oxaliplatin (a DNA replication inhibitor) and irinotecan (a topoisomerase I blocker) in adjuvant or metastatic (mCRC) regimens. Targeted therapies have been integrated into these regimens: anti-EGFR, cetuximab, and panitumumab (effective in RAS wild-type tumors). (Beretta et al., 2004; Braun & Seymour, 2011). Where it has been documented that the three-year overall survival rate of 5-FU-based regimens reaches 86% in patients with non-metastatic CRC with toxic effects such as neutropenia (54%), nausea (37%), neuropathy (38%), and anemia (33%), and with a 2-year overall survival rate with 5-FU-based regimens without Bevacizumab in metastatic colorectal cancer of up to 25% (Cunningham et al., 2009; Uncu et al., 2013).

Clinical evidence highlights that 5-FU-based regimens achieve a 3-year overall survival (OS) of 86% in non-metastatic RCC, although with relevant toxicity profiles: neutropenia (54%), peripheral neuropathy (38%), nausea (37%), and anemia (33%) (Beretta et al., 2004). In contrast, in mRCC, the

2-year OS with 5-FU without bevacizumab does not exceed 25%, reflecting the biological aggressiveness of advanced disease (Braun & Seymour, 2011).

BREAST CANCER

Breast cancer is a priority public health problem, as it is one of the leading causes of female mortality worldwide. Early detection and timely treatment substantially alter the natural history of the disease and improve patient prognosis (Zavala et al., 2019). Breast neoplasms are currently recognized as exhibiting marked heterogeneity, not only from a histological and epidemiological perspective but also in their molecular properties. These advances have allowed tumors to be classified into six molecular subtypes based on gene expression profiles of biomarkers such as ER, PR, claudins, HER2/NEU, PI3KCA, TP53, and MAP3K1, which has led to a more profound understanding of the mechanisms of tumor genesis and progression (Testa et al., 2020).

In the therapeutic setting, recent studies highlight the role of capecitabine in patients with advanced breast cancer who have not previously received taxanes and who are resistant to anthracyclines or have cardiac toxicity associated with these drugs. Its incorporation into adjuvant chemotherapy regimens has shown significant improvements in clinical outcomes, including in cases of metastatic cancer, with a positive impact on overall survival. However, its use in adjuvant settings is associated with an increased toxicity profile, which requires a rigorous evaluation of the risk-benefit balance (Cardoso et al., 2018; Natori et al., 2017).

USE IN OTHER NEOPLASMS

In the treatment of skin cancer, the use of oral capecitabine in combination with alpha interferon has been explored for the treatment of advanced squamous cell carcinoma, highlighting its favorable toxicity profile compared to other therapies (Waldman & Schmults, 2019). Clinical studies have assessed the efficacy of this drug in other skin malignancies, despite its primary approval for breast and colorectal cancer. For example, in patients with actinic keratosis, lesion control and regression have been observed, as well as promising clinical responses in cases of post-transplant squamous cell carcinoma administered at low doses (Blomberg et al., 2017; Rudnick et al., 2016). On the other hand, 5-FU is not currently considered a standard therapy for non-melanoma skin cancer. However, in patients with surgical contraindications who require systemic treatment, an adequate response has been documented as a therapeutic alternative in specific settings (Rudnick et al., 2016).

FLUOROPYRIMIDINES METABOLISM AND IDENTIFICATION OF POTENTIAL BIOMARKERS

The use of 5-FU and its analogues is associated with a risk of lethal toxicity in 0.5% of patients with advanced cancer and severe toxicity in up to 30%, which has prompted the search for genetic variants linked to toxic responses as the central axis of recent research (Leung & Chan, 2015). 5-FU, a structural analogue of uracil, is incorporated into RNA and DNA due to its similarity to natural pyrimidines (Blondy et al., 2020). Its intracellular transport is mediated mainly by SLC22A7 (with high affinity) and by ABC family transporters, also related to the response to fluoropyrimidine-based chemotherapy (Nies et al., 2015). Dihydropyrimidine dehydrogenase (DPD) catalyzes the initial degradation of 5-FU into dihydrofluorouracil (DHFU), which is sequentially metabolized to fluoro-β-ureidopropionate (FUPA) and fluoro-β-alanine (FBAL), the main route of drug elimination (Sharma et al., 2019; Thorn et al., 2011). The undegraded fraction is converted into fluorouridine monophosphate (FUMP) by orotate phosphoribosyltransferase (OPRT). FUMP is subsequently phosphorylated to fluorouridine triphosphate (FUTP) or dephosphorylated to fluorodeoxyuridine diphosphate (FdUDP) by ribonucleotide reductase (RR). Fluorodeoxyuridine monophosphate (FdUMP), a key metabolite, competitively inhibits thymidylate synthase (TYMS), impairing nucleotide synthesis and generating replication stress (Sharma et al., 2019; Thorn et al., 2011) (Figure 1).

5-FU-derived metabolites are directly linked to its cytotoxicity and could serve as biomarkers of individualized response: 1. Fluorodeoxyuridine triphosphate (FdUTP) induces abasic sites in DNA by activating the BER (base excision repair) system (Houghton et al., 1995; Noordhuis et al., 2004; Santi & McHenry, 1972; Van Triest et al., 2000). 2. FUTP, when incorporated into RNA, interferes with mRNA maturation, altering protein synthesis. (Van Triest *et al.*, 2000). 3. FdUMP inhibits TYMS, reduces dTMP production, and promotes the accumulation of dUTP, whose misincorporation into DNA triggers thymineless death (Houghton, Tillman and Harwood, 1995).

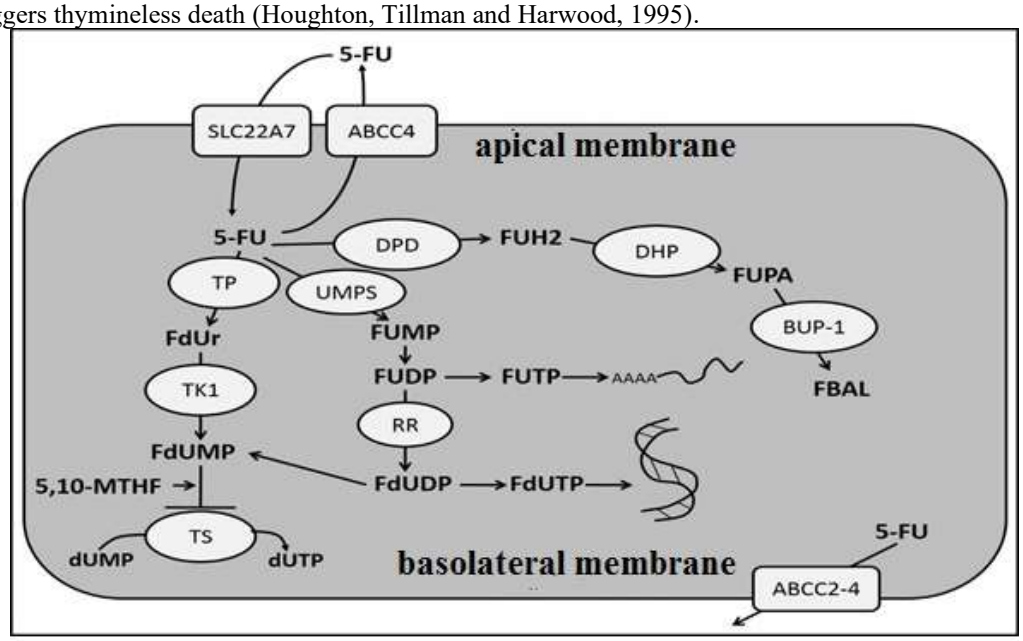

Figure 1. Metabolism and mechanism of action of 5-FU. SLC22A7 = Influx transporter. ABCC4, ABCC 2-4 = Efflux transporters. TP = thymidine phosphorylase, TK1 = thymidine kinase. TS = Thymidylate synthase. DPD = dihydropyrimidine dehydrogenase. DHP = Dihydropyrimidinase. BUP-1 = β-ureidopropionase. UMPS = Uridine monophosphate synthase/orotate phosphoribosyl transferase. RR = Ribonucleotide reductase. Metabolites are described in the body of the document. The truncated arrow indicates inhibition (Castro-Rojas, Ortiz-López and Rojas-Martínez, 2014).

GENOMIC BIOMARKERS ASSOCIATED WITH THE PHARMACOKINETICS AND PHARMACODYNAMICS OF 5-FU

This approach is based on the relationship between pyrimidine degradation metabolic pathways and fluoropyrimidine-induced toxicity. A key milestone was the report by Tuchman et al., who described severe toxicity in a patient with familial pyrimidinemia after exposure to 5-FU, suggesting a DPD enzyme deficiency (Tuchman *et al.*, 1985). Subsequently, it was confirmed that a 165-nucleotide deletion in the *DPYD* gene encoding DPD altered mRNA stability and reduced enzyme activity, being associated with an increased risk of toxicity (R *et al.*, 1995; G *et al.*, 1999). The enzymes dihydropyrimidine dehydrogenase (DPD) and thymidylate synthase (TS) have emerged as promising biomarkers for predicting toxicity and prognosis in patients treated with 5-FU. Pharmacogenomic studies have identified polymorphic variants in the genes of these enzymes, which explain the variability in therapeutic response and the occurrence of serious adverse effects (Shen *et al.*, 2015; Akhter and Rashid, 2019). These findings have prompted research into genomic biomarkers to personalize the use of fluoropyrimidines, optimizing efficacy and minimizing the risk of serious toxicity. These potential genomic biomarkers are listed below:

DIHYDROPYRIMIDINE DEHYDROGENASE ENZYME (DPD)

The enzyme dihydropyrimidine dehydrogenase (DPD) is responsible for the catabolism of pyrimidine bases, catalyzing the reduction of uracil and thymine to 5,6-dihydrouracil and 5,6-dihydrothymine, respectively, as part of the degradation of pyrimidines (Tuchman, 1993). In addition, it plays a critical role in the inactivation of 5-FU. As the rate-limiting enzyme in this pathway, it regulates the catabolism of both endogenous pyrimidines and exogenous fluoropyrimidines (Sharma, Gupta and Verma, 2019).

Genetic and Molecular Structure of DPD: The *DPYD* gene, located on chromosome 1p21.3, is over 840 kb long and contains 23 exons encoding a homodimeric protein of 1025 amino acid residues (Forouzesh and Moran, 2021). Each subunit of the enzyme consists of five functional domains: -Domain I (residues 27-172): Composed of α-helices and two [4Fe-4S] clusters. -Domain II (residues 173-286, 442-524): Flavin adenine dinucleotide (FAD)-binding site. -Domain III (residues 287-441): NADPH cofactor-binding site. -Domain IV (residues 525-847): TIM barrel fold that binds FMN and pyrimidine substrates. -Domain V (residues 1-26, 848-1025): Contains two additional [4Fe-4S] centers. Enzymatic activity requires hydrophobic interaction and hydrogen bonding between both subunits, forming an electron transport chain from NADPH to pyrimidine substrates (62%). This structure explains why DPD is only active as a dimer (Dobritzsch *et al.*, 2001; Forouzesh and Moran, 2021).

DPD Deficiency: Genetic Basis and Clinical Manifestations DPD deficiency, an autosomal recessive disorder (OMIM #274270), was initially described by Berger et al. in patients with excessive thymine uraciluria (Berger *et al.*, 1984; Quinonez and Thoene, 2020) (Berger *et al.*, 1984; Quinonez and Thoene, 2020). Its clinical presentation ranges from asymptomatic individuals (heterozygotes) to severe cases with seizures and neurological deficits (homozygotes). It is estimated that 0.2% of the population has complete deficiency and 2–6% have partial deficiency (Lu *et al.*, 1998; Mason *et al.*, 2009). In oncology, reduced DPD activity leads to toxic accumulation of 5-FU and its metabolites. Up to 31% of patients treated with 5-FU develop severe toxicity, and 59% of these cases are associated with enzyme deficiency (Lu *et al.*, 1998; AB *et al.*, 1999; van Kuilenburg *et al.*, 2000, 2001; Ezzeldin *et al.*, 2002; Ezzeldin and Diasio, 2004). A dramatic example was the lethal interaction between 5-FU and sorivudine in Japan, attributed to the inhibition of DPD by a metabolite of the antiviral agent (Haruhiro Okuda *et al*, 1997). More than 30 pathogenic variants in DPYD are associated with fluoropyrimidine toxicity. Four stand out for their robust clinical evidence: 1. c.1905+1G>A (DPYD*2A, rs3918290): Located in the splice donor site of exon 14, it generates a truncated mRNA and complete loss of enzymatic activity in homozygotes. It has a population frequency of 1.5% in Finland vs. <0.1% in African and Latin American populations (Chazal *et al.*, 1996; Mcmurrough and McLeod, 1996; JL *et al.*, 1997; AB *et al.*, 1999; van Kuilenburg *et al.*, 2001; Ezzeldin *et al.*, 2002). 2. c.2846A>T (rs67376798): Asp→Val (D949V) substitution in the catalytic domain V, reducing enzyme activity by 41% in vitro. Linked to severe hematological and gastrointestinal toxicity (Loriot *et al.*, 2018; Wörmann *et al.*, 2020). 3. HapB3 (rs75017182): Includes the intronic variant c.1129–5923C>G, which induces an aberrant splicing site, decreasing activity by 35%. Frequency 4.8% in Caucasians (Harris *et al.*, 1990; Jacobs *et al.*, 2016). 4. c.1679T>G (rs55886062): Ile→Ser (I560S) change in the FMN-binding domain, reducing activity by 75%. Frequency 0.1% in Europeans (Mcmurrough and McLeod, 1996; G and AL, 2002; Wörmann *et al.*, 2020). 5. Other variants of clinical interest: - Missense: c.1601G>A (p.Ser534Asn), c.2194G>A (p.Val732Ile) (Jiang *et al.*, 1997; Ikeguchi *et al.*, 2001; Baba *et al.*, 2003; Meulendijks *et al.*, 2015; M *et al.*, 2020). - Ethnic-specific: c.557A>G (p.Lys186Arg) in Afro-descendants (Loriot *et al.*, 2018; TJ *et al.*, 2021). - Deletions: c.295–298delTCAT, c.1897delC (AB *et al.*, 1999). - Nonsense: c.85T>C (p.Ser29Pro), c.703C>T (p.Arg235Ter), c.2658G>A (p.Lys886Lys), c.2983G>T (p.Gly995Ter) (AB *et al.*, 1999) (AB *et al.*, 1999). Rare variants account for 61.2% of *DPYD* functional variability, supporting the use of next-generation sequencing (NGS) for their detection (Toriumi *et al.*, 2004; E *et al.*, 2017; Takeyama *et al.*, 2018). DPYD genotyping is key to stratifying the risk of severe toxicity (neutropenia, mucositis) and adjusting fluoropyrimidine doses. DPD activity shows interindividual variability (up to

6-fold) without influence of age, sex, ethnicity, or smoking (Chazal *et al.*, 1996; Mcmurrough and McLeod, 1996; Lu *et al.*, 1998; G *et al.*, 1999). However, studies in mononuclear cells reveal intraindividual fluctuations over 24 hours, supporting the need for pretreatment plasma or enzyme monitoring (JL *et al.*, 1997). Guideline-based clinical recommendations (Loriot *et al.*, 2018; Wörmann *et al.*, 2020): -Genetic screening: Search for the four main variants to adjust doses or avoid fluoropyrimidines. -Uracilemia: Levels >16 ng/mL indicate dose reduction; levels >100 ng/mL contraindicate its use. -Chronotherapy: Continuous infusion of 5-FU adjusted to circadian rhythms to stabilize plasma levels (Harris *et al.*, 1990; G and AL, 2002; Jacobs *et al.*, 2016). These strategies are based on the lower activity of DPD in tumor tissue (vs. healthy tissue) (Jiang *et al.*, 1997; Ikeguchi *et al.*, 2001; Baba *et al.*, 2003), especially in colorectal cancer (Jiang *et al.*, 1997; Ikeguchi *et al.*, 2001), and its association with severe toxicity in unadjusted patients (Meulendijks *et al.*, 2015; M *et al.*, 2020; TJ *et al.*, 2021). Furthermore, DPD overexpression in gastric tumors correlates with 5-FU resistance and a worse prognosis (TORIUMI *et al.*, 2004). The integration of genotyping (DPYD), biomarkers (uracilemia), and circadian approaches optimizes the safety of fluoropyrimidine use. Although guidelines prioritize four variants, the genetic heterogeneity of DPD suggests expanding NGS analysis, especially in understudied populations. DPD pharmacogenomics remains a cornerstone for personalizing cancer treatments and minimizing risks.

THYMIDYLATE SYNTHASE ENZYME (TS)

The *TS* gene has been identified as a key candidate for relative resistance to 5-FU, where variants in its regulatory regions modulate gene transcription. High levels of intratumoral TS correlate with decreased sensitivity to the drug, while specific polymorphisms directly influence therapeutic efficacy (E *et al.*, 2017) (Table 1).

Table 1. TS-associated polymorphisms with direct involvement in the efficacy of fluoropyrimidine-based therapy

Type of metabolizer	**Based on genotype** (McMURROUGH and McLEOD, 1996; JL *et al.*, 1997)		**Based on phenotype** (Chazal *et al.*, 1996)	**Predicted DPD activity score** (Chazal *et al.*, 1996; McMURROUGH and McLEOD, 1996)	**Behavior** (Chazal *et al.*, 1996; McMURROUGH and McLEOD, 1996)
	Variants of interest	**DPD activity**	**Uracilemia measurement**		
	c.1129-5923C>G c.1905+1G>A	0.5			
	c.1679T>G c.2846A>T	0			
Normal metabolizer	Non-carriers		<16 ng/mL	2	Usual dose
Intermediate metabolizer	Heterozygous carriers		>16ng/mL	1-1.5	Score 1: Reduction 50% dosis Score 1.5: Reducción 25% dosis
Poor metabolizer	Compound heterozygous or homozygous carriers u		>100ng/mL)	0-0.5	Evaluate other treatment

Mechanism of action and resistance: The active metabolite FdUMP covalently inhibits the TS enzyme, blocking thymidylate synthesis and, consequently, DNA replication (Santi and McHenry, 1972; Takeyama *et al.*, 2018). Alterations in TS expression or structure (e.g., mutations that reduce affinity for FdUMP) compromise treatment response (Peters *et al.*, 2002). In colorectal cancer, for example, high intratumoral TS activity is associated with resistance to fluoropyrimidines, highlighting its potential as a prognostic marker (Takeyama *et al.*, 2018). Genetic variants with clinical impact: 1. 6-bp deletion in the 3'UTR: In advanced gastric cancer, patients carrying this variant showed improved disease progression and overall survival under 5-FU regimens, likely due to a reduction in TS expression (Keam *et al.*, 2008). 2. 5'UTR tandem repeats (VNTRs): 2R (2 repeats) and 3R (3 repeats) alleles regulate TS transcription. TS overexpression (associated with 3R) reduces the efficacy of 5-FU, while genotypes such as 2R/2R, 2R/3C, and 3C/3C are associated with improved survival in colorectal and gastric cancer (E *et al.*, 2017; Yoshikawa *et al.*, 2019). 3. Population distribution: The 3R/3R genotype is more common in Asian populations (67% in China vs. 38% in the United Kingdom), suggesting

ethnic differences in treatment response (S *et al.*, 1999; E *et al.*, 2008). Controversial clinical evidence: Although TS expression has been associated with decreased survival in lung, hepatocellular carcinoma, and pancreatic cancer (Fu *et al.*, 2019), its role is inconsistent: - In metastatic colorectal cancer, some studies report an inverse correlation between TS and survival under 5-FU (A *et al.*, 2004), while Noda et al. observed improved response to irinotecan-based regimens in tumors with high TS expression (NODA *et al.*, 2006). - In gastric cancer, TS variants did not show prognostic value with the S-1 analogue in a Japanese population, although they did show utility in predicting therapeutic benefit (S *et al.*, 1999). Despite discrepancies, TS genotyping is emerging as a promising tool for predicting response/toxicity. Priority variants include (Balboa-Beltrán *et al.*, 2015): - VNTR in 5'UTR (rs45445694): 2-9 repeats. - G>C SNP in the 3R allele (rs2853542): alters transcription factor binding. - 6-bp deletion in the 3'UTR (rs34489327): modulates mRNA stability. Current evidence supports the integration of TS biomarkers into precision oncology, although multicenter studies are needed to standardize their use in clinical guidelines.

METHYLENETRAHYDROFOLATE REDUCTASE ENZYME (MTHFR)

Methylenetetrahydrofolate reductase (MTHFR) converts 5-10 methylenetetrahydrofolate (5-10 MTHF) into 5-methylenetetrahydrofolate (5-MeTHF). It has been established that the optimal efficacy of 5-FU requires the intratumoral presence of 5-10 MTHF, which depends on the activity of MTHFR, where it is proposed that 5-10 MTHF associated with FdUMP generates a greater inhibition of TS, so that a lower activity of MTHFR theoretically leads to a greater inhibition of TS (Lin *et al.*, 2019). In a study conducted by Ramos et al., an association was found between the MTHFR variants C677T (rs1801133) and A1298C (rs1801131) and the occurrence of toxicity related to the use of fluoropyrimidines in a cohort of Costa Rican patients with metastatic colorectal cancer, which suggests an additional role as a biomarker for this gene; however, the role of its screening is not yet entirely clear (Ramos-Esquivel, Chinchilla and Valle, 2020). Although multiple variants have been described in the MTHFR gene, only two have been found to be related to reduced enzyme activity. In the case of c.677C> T, a greater thermolability of the enzyme has been found, which generates a reduction in its activity by 70% for heterozygous carriers and 35% for homozygous carriers. For c.1298A> C, a decrease in activity has also been reported, but to a lesser extent (Yeh *et al.*, 2017). Other variants described are c.1298A> C and c.1286A> C, which are associated with the development of toxicity and a poor prognosis when treated with 5-FU (F *et al.*, 2011; K *et al.*, 2011).

THYMIDINE KINASE 1 ENZYME

It has been found that with the inhibition of TS, the activity of thymidine kinase 1 (TK1) increases, suggesting a mechanism associated with the rescue kinetics seeking to improve the mechanisms of thymidine uptake, where it has been found that 24 hours after the start of treatment with 5-FU, an increase in the expression of TK1 is seen, which suggests this protein can be used as a biomarker to evaluate the inhibition of TS (Lee *et al.*, 2010). From a biological point of view, it is known that this enzyme plays an important role in the S phase of the cell cycle, is present in the synthesis of thymidine monophosphate (TMP), and participates in the phosphorylation of fluorodeoxyuridine (FdUrd), which leads to the production of the pharmacologically active metabolite of 5-FU, which is why its activity is related to the inhibition of TS, seeing a change in activity in tumor tissues vs. healthy tissues; however, its biological use is still unclear (Kenji Dohden, Kenji Ohmura and Yoh Watanabe, 1993; Sakamoto *et al.*, 2015).

ENZYMES OF THE PYRIMIDINE SYNTHESIS AND SALVAGE PATHWAYS

Enzymes involved in pyrimidine salvage and biosynthesis influence cancer chemotherapy based on pyrimidine antagonists such as 5-FU, capecitabine, and tegafur. Their function is closely linked to the activity of pyrimidine synthesis enzymes, including dihydropyrimidine dehydrogenase (DPD), thymidylate synthase (TS), uridine phosphorylase (UP), thymidine phosphorylase (TP), uridine

monophosphate kinase (UMPK), and orotate phosphoribosyl transferase (OPRT), since their cellular expression levels depend on the activity of these enzymes in cancer cells, suggesting a role in sensitivity and resistance to these drugs (Kim et al., 2009). It has been found that the intratumoral levels of expression of thymidine phosphorylase and dihydropyrimidine dehydrogenase correlate with the response to capecitabine and doxifluridine, thus predicting the response to these drugs, suggesting their clinical use instead of categorizing patients as responders and non-responders. A positive correlation has also been found between the expression of other enzymes of de novo pyrimidine synthesis, such as OPRT, TMPK, UMPK, and UMPK/CMPK, together with the enzyme cytidine deaminase (CD) in the face of chemosensitivity to 5-FU (Yasuno et al., 2013).

URIDINE PHOSPHORYLASE ENZYME (UP)

Uridine phosphorylase is an enzyme that is part of the pyrimidine salvage pathway by adding ribose or deoxyribose to pyrimidine bases, forming uridine or thymidine, which is why this enzyme plays an important role in DNA synthesis. Two isoforms have been described: uridine phosphorylase I (UP1) and uridine phosphorylase II (UP2) (YT et al., 2020). It has been found that ATP plays a role in the function of uridine phosphorylase in Escherichia coli, where ATP alters the folding of the enzyme, modifying its enzymatic activity. It has been found that the increase in the concentration of ATP in cancer cells confers resistance to the drug 5-FU derived from the loss of enzyme activity and the biotransformation of the drug (YT et al., 2020).

It has been found that the differential expression of this enzyme in tumor tissue and healthy tissue is one of the factors involved in the chemosensitivity and cytotoxic effect of 5-FU, where it has been found that the activity of this enzyme is positively regulated by oncogenes, tumor suppressor proteins, and cytokines, contrary to what happens to its homologous enzyme, thymidine phosphorylase (TP), which is reduced in tumor tissues (Pizzorno et al., 2002). In a study conducted by Cao et al. in which a knockout mouse model for the UP-/- enzyme was used, a lower incorporation of 5-FU into nucleic acids was found, as well as its role in the activation of 5-FU, given that it was found that the deficiency in the activity of the enzyme alters the pharmacokinetic profile of the drug, increasing its clearance (Cao et al., 2002). It has also been suggested that the main therapeutic activity of 5-FU is associated with DNA damage, and many toxic side effects are mainly related to the incorporation of FUTP into RNA, where the production of this metabolite is mediated by the activity of the UP enzyme, so apart from the role of this enzyme at the level of the cytotoxic effect of fluorouracil, its role in the appearance of adverse events and as a marker against the use of cytoprotective agents such as uridine has also been raised, where these are used as an enzyme inhibition strategy as a prevention and treatment measure (Renck et al., 2013).

OROTATE PHOSPHORIBOSYLTRANSFERASE ENZYME (OPRT)

Orotate phosphoribosyltransferase is an enzyme that is present in de novo pyrimidine synthesis, where it helps catalyze the formation of orotate 5'-monophosphate (OMP) (Hozumi et al., 2015). Within the uridine 5'-monophosphate synthetase gene, a bifunctional enzyme is encoded where the N-terminal domain has the orotate phosphoribosyltransferase (OPRT) function and the C-terminal domain has the orotidine 5'-monophosphate decarboxylase function (P et al., 2018). The OPRT enzyme has been identified as the main enzyme responsible for the phosphoribosylation of 5-FU in the presence of phosphoribosyl pyrophosphate (PRPP) in colorectal tumor tissue, where this enzyme commonly presents a higher activity compared to non-tumor tissue and has been assigned the rate-limiting step in the activation of 5-FU (S et al., 2007). In fact, higher OPRT enzyme expression has been associated with a better response to 5-FU-based treatment in CRC patients in terms of disease-free survival as well as a lower incidence of side effects, thus being proposed as a predictive marker of efficacy for this agent (W et al., 2003; S et al., 2013). A correlation has been found between high tumor-level OPRT expression and increased sensitivity to 5-FU in urinary bladder, gastric, and colorectal cancer. Likewise, it has been

shown that combined therapies with S-1 for malignant pleural mesothelioma refractory to pemetrexed are highly effective in tumors with high OPRT expression (Hamamoto et al., 2016; K et al., 2019).

Using preclinical models, it has been shown that low DPYD enzyme expression and high OPRT enzyme expression are associated with increased sensitivity of colorectal tumors to 5-FU (KINOSHITA et al., 2007). These results are reflected in the clinical context, where low DPYD enzyme expression, as well as high OPRT enzyme expression or activity in tumor tissue, appear to be associated with a better prognosis for patients with resectable CRC in the adjuvant setting and for patients with metastatic CRC receiving 5-FU-based therapy (W et al., 2003; T et al., 2006; Yamada, Linuma, and Watanabe, 2008). Supporting this hypothesis, a prospective clinical study by Ochiai et al. on a cohort of patients with CRC showed that those with higher OPRT/DPYD expression ratio values in tumor tissue samples had a better prognosis (5-year disease-free survival and overall survival) in response to treatment with 5-FU (T et al., 2014).

THYMIDINE PHORPHORYLASE ENZYME (TP)

Thymidine phosphorylase (TP) is responsible for reversibly catabolizing thymidine, deoxyuridine, and its analogues to thymine uracil in the presence of phosphate, where in the case of 5FU, it is converted into fluorodeoxyuridine (FdU) by thymidine phosphorylase (TP) and then converted into FdUMP by thymidine kinase (TK) (T et al., 2018; Mori et al., 2019). It has been shown that the TP enzyme is indistinguishable from platelet-derived endothelial cell growth factor (PD-ECGF), which is why it has demonstrated angiogenic effects and is of great interest for its trophic effects on tumor tissue, as well as its role in the clinical response to 5-FU, where it would have dual action as an angiogenic factor and, therefore, pro-tumorigenic and as a pro-activator of 5-FU (JG et al., 2005; T et al., 2018), which is why it is proposed that the decrease in TP and the increase in TS levels can be considered as the main factors involved in the development of resistance to 5-FU (Mori et al., 2019).

URIDINE MONOPHOSPHATE KINASE ENZYME (UMPK)

The UMPK enzyme has been linked to the acquired resistance of colorectal tumor cells to 5-FU. It is an enzyme involved in the generation of FdUTP from 5-FU. A decrease in the expression levels of the enzyme would lead to a decrease in the incorporation of FdUTP into DNA and consequently to a lower cytotoxic response of tumor cells (R et al., 2009). Different variants in the genes that code for these enzymes have been associated with alterations in their activity, which may result in ineffective or toxic responses to treatment with 5-FU and analogous compounds (JG et al., 2005).

DIHYDROPYRIMIDINASE (DPYS) AND B-UREIDOPROPIONASE (UPB1) ENZYMES

The highest enzymatic activities of the enzymes dihydropyrimidinase and β-ureidopropionase have been detected at the physiological level in the liver and kidneys, which is why these organs are considered to be the main ones responsible for the catabolism of pyrimidines at the systemic level. In this way, while in the liver the final product of uracil catabolism through this pathway is, between 70% and 100%, the compound β-alanine, in extrahepatic tissues the final product is dihydrouracil (Kuilenburg, Lenthe, and Gennip, 2006). It is noteworthy that when comparing the activity of all enzymes in relation to tumor and non-tumor tissues, in all tumor tissues analyzed there is greater activity of the dihydropyrimidinase enzyme than in its non-tumor counterparts. Largely because of this, solid tumors resemble the liver in that they carry out the entire catabolic process until the formation of β-alanine as the end product, unlike their non-tumor counterparts (Naguib, el Kouni, and Cha, 1985). There are few reports of fluoropyrimidine toxicity due to variants in the DPYS gene. The existence of a rare missense variant in exon 5 of the DPYS gene (DPYS 833G>A), which results in a complete loss of enzyme activity, has been associated with lethal 5-FU toxicity in a patient with breast cancer (van Kuilenburg et al., 2001). Another variant also present in this patient, DPYS c.-1T>C, has been

associated with an increased risk of gastrointestinal toxicity from fluoropyrimidine administration (Fidlerova et al., 2009).

FLUOROPYRIMIDINES TRANSPORTERS

Two types of transporters allow the flow of pyrimidine nucleosides into cells: the equilibrative nucleoside transporter system (ENT-1/SLC29A1 and ENT-2/SLC29A2) and the concentrating nucleoside transporter system (CNT-1/SLC28A1 and CNT-3/SLC28A3). The former are abundant in tumor tissues, whereas the latter are frequently absent (Cao et al., 2011). A negative correlation between the expression (regarding mRNA) of the proteins SLC22A2, SLC23A2, and ABCB1 and a positive correlation between the ABCC2 protein and chemosensitivity to 5-FU in adenocarcinoma and esophageal squamous cell carcinoma lines have been shown (153). Although the functional significance of this correlation remains to be verified, these results demonstrate the possible involvement of these proteins in the transport mechanism of 5-FU to and from tumor cells. The participation of the ABCC5 protein in the transport mechanism (efflux) of 5-FU in colon cancer and breast adenocarcinoma cells has been better studied, demonstrating that it is capable of mediating the transport of 5-FU and its monophosphorylated metabolites and of conferring resistance to these in cells that overexpress it (Pratt et al., 2005).

DISCUSSION

Cancer remains one of the diseases that generates the greatest interest in the public health field, given that despite great efforts in the search for more effective treatments and therapeutic targets, it remains one of the leading causes of death worldwide. With the development of omics sciences, a greater understanding of the individualized pathophysiological process has been achieved, as well as progress in the establishment of effective personalized pharmacological therapies and the identification of patients at higher risk of adverse events to limit treatment discontinuation, which directly impacts the outcome of the disease. In the specific case of fluoropyrimidines, which have demonstrated their clinical utility over time, a major limitation has been the appearance of severe toxicity events and episodes of therapeutic inefficacy despite management according to management guidelines. This is the reason why numerous studies have already been conducted to assess strategies for the individualization of drug therapy. Pharmacogenomics is one of the strategies that has been able to identify the potential causes of the diversity of response among populations.

The identification of potential biomarkers associated with treatment with these chemotherapeutic agents raises the possibility of interindividual management, allowing for the early identification of patients who may have a better response and thus enhance the anticancer effect already demonstrated by this group of drugs. Furthermore, information can be generated about patients at greatest risk of adverse events, leading to their identification. This already provides a solid scientific basis, with some organizations dedicated to pharmacogenomics already developing recommendations for phenotype and genotype recognition for individualized dosing.

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For now, the way is to identify the prevalence of genetic variants in the various populations as a mechanism to evaluate their genetic contribution according to ancestry to the risk of toxicity and the

appearance of therapeutic failure (ML et al., 2009). Haplotype association studies, as well as direct genotyping of patients from the sequencing of treatment response genes, would allow establishing their real prevalence based on the genotypic frequencies of said genomic biomarkers in each population under study associated with their validation in the clinical context, for which genotype-phenotype correlation studies in clinical trials are essential to elucidate the real relevance of said genomic biomarkers in the response to treatment (Candelaria *et al*, 2006).

Finally, in the case of fluoropyrimidines, this document presents all the possible markers involved in evaluating their response and toxicity, all of this focused on the use of pharmacogenomics as a tool for the treatment of prevalent chronic diseases such as cancer, which in the long term will generate an impact on the treatment of patients and ultimately on public health in the face of a reduction in mortality rates associated with cancer treatment.

ACKNOWLEDGMENTS
We thank all the individuals and institutions that contributed to this work, especially for their technical and financial support.

CONFLICT OF INTEREST
None.

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