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Genetic polymorphisms associated with toxicity in treatment with 5-fluorouracil in patients with colorectal cancer: A systematic review

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Abstract

Introduction: Colorectal cancer is the most common malignancy of the digestive tract. The treatment is based on administering antitumor medications, such as 5-fluorouracil (5-FU), which is an antimetabolite and antineoplastic agent. However, it has been shown that there is toxicity related to genetic polymorphisms in patients treated with 5-FU, including gastrointestinal symptoms, myelosuppression, and neurotoxicity. The genetic variations of four genes have been studied, including ABCB1, DPYD, MTHFR, and TYMS.

Methodology: Bibliographic review based on digital articles, starting with the research of information approximately 5-fluorouracil as treatment of patients with colorectal cancer, its adverse reactions, polymorphisms, and toxicity. The database used is PubMed, ScienceDirect, and Scielo, published within the last ten years. It included scientific articles and studies on patients older than 18. Publications in Spanish and English as well as full-text articles. Additionally, the polymorphisms were analyzed in the NCBI (National Center for Biotechnology Information) database, from which the allelic frequencies at the global and Latin American levels were obtained.

Results: A total of 11 articles were reviewed, from which we obtained data about polymorphisms that developed in patients with colorectal cancer who received treatment with 5-fluorouracil. The analyzed genes were ABCB1, DPYD, MTHFR, and TYMS. It was established that the polymorphisms trigger toxicity that manifests in different forms: diarrhea, stomatitis, mucositis, and neutropenia.

Keywords:
DeCS: "5-fluorouracil", "5-FU", "Colorectal cancer", "Colorectal neoplasms", "Genetic polymorphisms".

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Introduction

Approximately 1 to 2 million people worldwide have been diagnosed with colorectal cancer (CRC) each year, and it is essential to note that more than 600,000 people die from this disease. Despite vital hereditary components, most cases of colorectal cancer are sporadic, developing slowly over several years through the adenoma-carcinoma sequence [1].

The treatment of choice for localized RCC is surgery; however, treatment with chemotherapy supported by fluoropyrimidines can be performed. Fluoropyrimidines are antimetabolites, thus constituting a family of antitumor molecules [2]. Its mechanism of action is based on inhibiting the synthesis of DNA constituents preventing cells from carrying out DNA replication. Within this pharmacological group is 5-fluorouracil (5-FU), a drug used as an essential component of systemic chemotherapy for colorectal cancer in palliative and adjuvant settings [3].

Its mechanism of action is complex; it acts after the activation of fluorodeoxyuridine monophosphate (FdUMP) at the level of thymol. Synthase (TS) is an enzyme that allows the addition of a methyl group at position five at the deoxyuridine level monophosphate (dUMP) to transform it into 5-deoxythymidine monophosphate (dTMP). If a 5-FU molecule replaces uracil, TS cannot add this methyl group, and DNA synthesis cannot occur due to thymidylic acid deficiency. Furthermore, 5-FU can be activated to fluoridine triphosphate (FUTP) and incorporated into RNA, representing another cytotoxicity mechanism [4].

Treatment with these drugs is generally well tolerated, except in a small percentage of patients who develop severe life-threatening toxicity. The clinical presentation of this toxicity is similar to a 5-FU overdose and includes myelosuppression, mucositis, stomatitis, diarrhea, skin changes, and neurological abnormalities [5].

CRC is caused by mutations that target oncogenes, tumor suppressor genes, and genes related to DNA repair mechanisms. Genetic polymorphisms in the ABCB1, DPYD, MTHFR, and TYMS genes can result in decreased or lost enzyme activity, accumulating drugs, their metabolites, and potential toxicity [6].

Materials and methods

Study design

A descriptive study was carried out through a bibliographic review based on digital journals, including studies published during the last ten years.

Databases analyzed

The databases used were PubMed, ScienceDirect, and Scielo, the same ones that allowed the collection of information from scientific articles, systematic reviews, and clinical trials about the use of 5-fluorouracil as a treatment in patients with colorectal cancer, adverse reactions, polymorphisms, and toxicity. Additionally, polymorphisms were analyzed in the NCBI database (National Center for Biotechnology Information), from which the allelic frequencies at the global and Latin American levels were obtained.

Search Terminology

The search in the databases was carried out in English and Spanish, including key terms such as "5-Fluorouracil", "5-FU", "Cáncer colorectal," and "Genetic Polymorphism "using the operators "and," " or " and " not". In this way, the advanced search was carried out with the following terminology:
(("5-FU" OR "5-Fluorouracil") AND ("Cancer of Rectum" OR "Rectal Cancer" OR "Rectal Tumors" OR "Cancer of the Rectum" OR "Neoplasms Rectal" OR "Rectum Cancer")) AND ("Genetic Polymorphism" OR "Polymorphism (Genetics)" OR "Genetic Polymorphisms" OR "Polymorphisms, Genetic").

Inclusion criteria

Scientific articles, journals in Spanish and English, and visible full-text articles that study and analyze the use of 5-fluorouracil as a treatment in colorectal cancer and the appearance of adverse reactions from genetic polymorphisms; these studies must be carried out in patients older than 18 years of age.

Exclusion criteria

Scientific articles that are not related to the subject, scientific articles that mention another type of treatment for colorectal cancer, and studies that include patients under 18 years of age.

Selection of articles

All the articles exposed by the databases that met the search parameters were selected and entered into the "Rayyan QCRI" software. This application allowed us to choose the articles of interest through a thoughtful review, considering the following parameters: 1) Title. 2) Summary. 3) Results. 4) Type of study. 5) Inclusion and exclusion criteria. In this way, the study was accepted or rejected by employing the qualifications "included," "excluded," or "excluded after full revision."

Universe and sample

With the initial search, 50 articles were obtained; when entering the data into the software and analyzing the title, abstract, and results, they were selected as follows:

- Eleven articles that mention genetic polymorphisms in patients older than 18 years with colorectal cancer who presented adverse reactions after administering 5-fluorouracil were included.

- Excluded: 15 articles that refer to another type of cancer (gastric cancer, breast cancer), studies in which other treatment schemes were applied, and studies in the pediatric population.

- Excluded after full review: Twenty-four articles mentioning 5-FU treatment combined with other drugs, including the 5-FU prodrug (capecitabine).

Data Collection

The 11 selected articles were read and analyzed in full text to extract the necessary information displayed in the results tables, highlighting the following parameters: author, gene, polymorphism variants, global frequency (NCBI), Latin American frequency 2, adverse reactions, and study population.

Results

Study participants

The systematic review presents a summary of 11 articles (Table 1).

Table 1. A. Genetic polymorphisms associated with toxicity in treatment with 5-fluorouracil patients with colorectal cancer."

Article	gene	Variant	Function	phenotype	allele	Frequency (NCBI) Global	Frequency (NCBI) Latin America	Study population	Reference
ABCB1 gene polymorphisms are associated with adverse reactions in fluoropyrimidine-treated colorectal cancer patients.	ABCB1 (Transporter gene ATP-binding cassette B1)	rs1128503	P-glycoprotein transporter Missense	It does not correlate with long-term prognosis in patients with stage II-B or III-C CRC treated with 5-FU.	A>G	*A=0.426598 **S=0.573402	*A=0.4756 **S=0.5244	67 patients from Hospital Gregorio Marañón (Madrid, Spain), older than 18 years and diagnosed with colorectal cancer, were taking 5-FU.	(Gonzalez-Haba et al., 2010) [7].
		rs2032592	Missense		A>G	*A = 0.99361 **S = 0.00639	*A = 0.9986 **S = 0.0014		
		rs1045642	Missense	Does not correlate with early relapse in patients with high-risk stage II and III colorectal cancer	A>G	*A=0.506833 **S=0.493167	*A=0.4520 **S=0.5480		
Combinations of polymorphisms in genes involved in the 5-Fluorouracil metabolism pathway are associated with gastrointestinal toxicity in chemotherapy-treated colorectal cancer patients.	DPYD	rs3918290	Missense	DPYD deficiency	C > T	*C=0.995705 **T=0.004295	*C=0.9986 **T=0.0014	Two cohorts of 161 and 340 patients, exploration and validation cohort, respectively. Similarly, treated with adjuvant 5-FU-based chemotherapy.	(Afzal et al., 2011) [8].
		rs2297595	Missense	DPYD deficiency	T > C	*T = 0.908329 **C = 0.09167	*T = 0.9593 **C = 0.0407		
		rs1801159	Missense	DPYD deficiency	T>C	*T = 0.800699 **C = 0.19930	*T = 0.6995 **C = 0.3005		
		rs1801265	Missense	DPYD deficiency	A > G	*A = 0.781414 **S = 0.21858	*A = 0.7728 **G = 0.2272		
	MTHFR	rs1801133	Missense variant	MTHFR deficiency	G>A	*G=0.659842 **A=0.340158	*G=0.5473 **A=0.4527		
		rs1801131	Missense variant	MTHFR deficiency	T>G	*T=0.695830 **S=0.304170	*T=0.8080 **S=0.1920		
	TYMS	rs45445694	Variant 5 Prime UTR	TYMS deficiency	deletion	GCC...=0.7507	GCC... =1.0		

Table 1. B. Genetic polymorphisms associated with toxicity in treatment with 5-fluorouracil patients with colorectal cancer."

Article	gene	Variant	Function	phenotype	allele	Frequency (NCBI) Global	Frequency (NCBI) Latin America	Study population	Reference
Methylenetetrahydrofolate reductase genetic polymorphisms and toxicity to 5-FU-based chemoradiation in rectal cancer.	MTHFR	rs1801133	Missense	MTHFR deficiency.	G > A	*G = 0.659842 **A = 0.34015	*G = 0.5473 **A = 0.4527	131 patients older than 18 years, treated with 5-FU.	(Thomas et al., 2011) [9].
		rs1801131	Missense	MTHFR deficiency.	T>G	*T=0.695830 **S=0.304170	*T=0.8080 **S=0.1920		
DMET™ (Drug-Metabolizing Enzymes and Transporters) microarray analysis of colorectal cancer patients with severe 5-fluorouracil-induced toxicity.	DPYD	rs3918290	DPYD: splice donor variant	TYPE OF VARIATION SNV single nucleotide variation	C > T	*C = 0.995705 **T=0.004295	*C=0.9987 **T=0.0013	1,936 genetic variants are distributed in 231 genes involved in the metabolism, excretion, and transport of 5-FU.	(Rumiato et al., 2013) [10].
Potential of dihydropyrimidine dehydrogenase genotypes in personalizing 5-fluorouracil therapy among colorectal cancer patients.	DPYD	rs1801159	Missense	SNV single nucleotide variation	T>C	*T = 0.800699 **C = 0.19930	*T = 0.6995 **C = 0.3005	26 patients (Malaysian, Chinese and Indian) with CRC and treated with 5-FU chemotherapy.	(Teh et al., 2013) [11].
		rs17376848	Missense	SNV single nucleotide variation	A > G	*A = 0.958038 **S = 0.04196	*A=0.9223 **S=0.0777		
Genetics polymorphisms in 5-Fluorouracil-related enzymes predict pathologic response after neoadjuvant chemoradiation for rectal cancer.	TYMS	rs2853542	TYMS: Variant 5 Prime UTR	SNV single nucleotide variation	G > A/□ G > C/□ G > T	*G = 1.0000 **C = 0.0000 **T = 0.0000	*G = 1,000 **C = 0.000, **T = 0.000	50 patients with CRC who received neoadjuvant therapy with 5-FU.	(Nelson et al., 2016) [12].

Table 1. C. Genetic polymorphisms associated with toxicity in treatment with 5-fluorouracil patients with colorectal cancer."

Article	gene	Variant	Function	phenotype	allele	Frequency (NCBI) Global	Frequency (NCBI) Latin America	Study population	Reference
5-fluorouracil toxicity in the treatment of colon cancer associated with the genetic polymorphism 2846 A>G (rs67376798)	DPYD	rs67376798	Missense	Response to fluorouracil - Toxicity/ADR, metabolism/pharmacokinetics.	T>A	*T = 0.994834 **A = 0.00516	*T = 0.997 **A = 0.003	A 72-year-old female patient was diagnosed with CRC and treated with 5-FU.	(González-Perera et al, 2017) [13].
Thymidylate synthase gene variants as predictors of clinical response and toxicity to fluoropyrimidine-based chemotherapy for colorectal cancer.	TYMS	rs45445694	Variant 5 Prime UTR		Indel insertion and removal	*GCC... = 1.00 **CCGCGCCA CTT= 0.00	*GCC... = 1.00 **CCGCGCCA CTT= 0.00	99 Mexican patients with advanced CRC (stages III-IV) who received 5-FU.	(Castro-Rojas et al., 2017) [14].
		rs2853542	Variant 5 Prime UTR		G>A/G>C/G>T	*G=1.0000 **C=0.0000, **T=0.0000	*G=1,000 **C=0.000, **T=0.000		
DPYD*2A and MTHFR C677T predict toxicity and efficacy in patients on chemotherapy with 5-fluorouracil for colorectal cancer.	DPYD	rs3918290	Splice donor variant	Dihydropyrimidine dehydrogenase deficiency. Response to fluorouracil - Toxicity/ADR, Metabolism.	C > T	*C = 0.995705 **T = 0.004295	*C = 0.9987 **T = 0.0013	161 Bangladeshi CRC patients were treated with 5-FU.	(Nahid et al., 2018) [15].
	MTHFR	rs1801133	Missense	MTHFR deficiency.	G > A	*G = 0.659842 **A = 0.34015	*G = 0.5473 **A = 0.4527		
Evaluation of adverse effects of chemotherapy regimens of 5-fluoropyrimidines derivatives and their association with DPYD polymorphisms in colorectal cancer patients.	DPYD	rs3918290	Splice donor variant	DPYD deficiency Response to fluorouracil - Toxicity/ADR, Metabolism.	C > T	*C = 0.995705 **T = 0.004295	*C = 0.9987 **T = 0.0013	88 Iranian CRC Patients Randomly Received 5-FU, Mazandaran.	(Negarandeh et al., 2020) [16].

Table 1. D. Genetic polymorphisms associated with toxicity in treatment with 5-fluorouracil patients with colorectal cancer."

Article	gene	Variant	Function	phenotype	allele	Frequency (NCBI) Global	Frequency (NCBI) Latin America	Study population	Reference
The Role of Dihydropyrimidine Dehydrogenase and Thymidylate Synthase Polymorphisms in Fluoropyrimidine-Based Cancer Chemotherapy in an Iranian Population.	DPYD	rs3918290	Splice donor variant	DPD deficiency. Response to fluorouracil - Toxicity/ADR, Metabolism.	C > T	*C = 0.995705 **T = 0.004295	*C = 0.9987 **T = 0.0013	83 cancer patients received 5-FU-based chemotherapy at Hazrat - e Rasool hospital and Masoud clinic, Tehran, Iran, between February 2014 and June 2016.	(Abbasian et al., 2020) [17].
		rs55886062	Missense	Response to fluorouracil – Toxicity. DPD deficiency.	A > C	*A = 0.999371 **C = 0.00062	*A = 1,000 **C = 0.000		
		rs67376798	Missense	Response to fluorouracil - Toxicity/ADR, metabolism/pharmacokinetics.	T > A	*T = 0.994834 **A = 0.00516	*T = 0.997 **A = 0.003		
	TYMS	rs45445694	Variant 5 Prime UTR	TYMS deficiency	Indel insertion and removal	*GCC...= 1.00 **CCGCGCCACTT= 0.00	*GCC... = 1.00 **CCGCGCCACTT= 0.00		

* Reference allele: percentage of the normal allele in the patients.
** Alternative allele: percentage of the mutated allele in the patients.
Global frequency: total population analyzed (1000 genes) according to the NCBI database.
Latin American Frequency 2: subgroup that analyzes a specific population, individuals with mainly European and American ancestry.
CCG...: CCGCGCCACTTGGCCTGCCTCCGTCCCGCCGCGCCACTTGGCCTGCCTCCGTCCCGCCGCGCCACTT

Discussion

Brambila-Tapia [18] indicates that the ABCB1 gene is fundamental in the bioavailability and limitation of cell toxicity of a wide range of drugs and xenobiotics, including 5-FU.

According to Gonzalez-Haba et al. [7], the study "ABCB1 gene polymorphisms are associated with adverse reactions in fluoropyrimidine-treated colorectal cancer patients" demonstrated the existence of three variants: rs1045642, rs1128503, and rs2032592 in the ABCB1 gene. A change from A to G is related to the following adverse reactions: neutropenia, diarrhea, and hand-foot syndrome. Based on these criteria, 41.8% of patients were found to have moderate to severe neutropenia while taking 5-FU; in addition, 28.4% had moderate to severe diarrhea.

The rs1045642 variant of the ABCB1 gene was statistically associated with diarrhea in patients on a 5-FU-based regimen (P = 0.037), thus presenting a risk.

According to the database that has been analyzed in NCBI, it has been established that for the rs1045642 variant, the global frequency of the significant or reference allele adenine is present at 50.7%, and the minor or alternative allele guanine is present in 49.3% of the universal population. Similarly, studies conducted on Latin American individuals with primarily European and American ancestry have been reported in the Latin American 2 subgroup, where the frequency of this variant corresponds to 45.2% and 54.8% for adenine and guanine, respectively [7].

Analyzing a German population, Sainz et al. [19] confirmed that male carriers of the A (adenine) allele are less likely to develop CRC. It is estimated that this variant may influence ABCB1-mediated estrogen efflux from colonic epithelial cells and thus lead to a lower risk of developing CRC (OR = 0.85, 95% CI: 0.74-0.97). However, in the study of Mrozikiewicz-Rakowska et al. [7], in a Polish population, it was established that the SNP rs1045642 of the G (guanine) allele is more frequent in males and thus becomes a vulnerable group to developing CRC. This frequency suggests that the polymorphism may be involved in CRC pathogenesis in a sex-specific manner; thus, further population studies are needed to explore this association.

Regarding the rs1128503 variant, the overall NCBI frequency for the major adenine allele is 42.7% and for the minor guanine allele 57.3%; being associated with a higher incidence in guanine compared to the variable mentioned above; the frequency at the Latin American level 2, is presented in a similar way to the previous variant, in which the incidence predominates in guanine with 52.4% and adenine 47.6%. Gonzalez-Haba et al. [7] indicated that this variant is not associated with long-term prognosis in patients with CRC. Similarly, de Castro et al. [20, 21] conducted a study in a Brazilian population (n=121) and found that this polymorphism correlates with a lower risk of developing CRC (P = 0.0001; OR = 0.16; 95% CI = 0.06-0.41).

Last, the rs2032592 polymorphism analyzed in the study by Gonzalez-Haba et al. [7] showed that it is not associated with long-term prognosis in patients with stage II-B or III-C colorectal cancer treated with 5-FU. However, genetic variations in the ABCB1 gene are related to the incidence of neutropenia, diarrhea, and hand-foot syndrome in colorectal cancer patients treated with fluoropyrimidines.

Martinelli et al. [22] and Gonzalez-Haba et al. [7] found that polymorphisms rs1045642, rs1128503, and rs2032592 of the ABCB1 gene had no impact on CRC risk. The authors agree that the results need to be validated in a larger population for this finding to be representative.

The second gene analyzed is dihydropyrimidine dehydrogenase "DPYD". Abbasian et al. [17] indicated that DPYD is responsible for the conversion of 5-FU to 5-fluorodihydrouracil (5-FUH2) and plays a crucial role in 5-FU catabolism. Functional single nucleotide polymorphisms (SNPs) in the DPYD gene alter DPD activity, leading to the development of severe 5-FU-related toxicities [17].

Within this review, seven variants were established; the most relevant correspond to rs3918290, rs55886062, and rs67376798, associated with a decrease in DPYD activity and a high risk of severe toxicity due to 5-FU. The development of severe toxicity leads to dose reduction, treatment discontinuation, and even death in patients with colorectal cancer. Lunenberg et al. [22, 23] mention that the decrease or absence of the metabolic activity of DPYD induces an increase in the intracellular concentrations of active metabolites of 5-FU, such as fluorodeoxyuridine monophosphate (FdUMP), which increases the risk of toxicity such as diarrhea, hand-foot syndrome, mucositis and myelosuppression.

The study carried out by Nahid et al. [15], including 161 Asian patients, showed that the most relevant polymorphism, rs3918290, is significantly associated with anemia (P =0.042), neutropenia (P =0.018), thrombocytopenia (P =0.050), nausea (P =0.012) and diarrhea (P =0.026). On the other hand, Lee et al. [24] reported an incidence of rs3918290 treated 2886 Caucasian patients with 5-FU-containing regimens. In 33.1% of patients, serious side effects were due to 5-FU, and 88% of patients with the rs3918290 polymorphism experienced severe side effects compared with patients without this polymorphism (57.1% vs. 18.1%). Common symptoms reported were diarrhea (12%), neutropenia (11.7%), nausea and vomiting (5%), fatigue (4.9%), and mucositis (4.2%). Compared to the findings of Negarandeh et al. [16], who indicated that this polymorphism was found with a higher incidence in 88 Iranian patients who were included in the study, all of whom had diarrhea (24.7%), nausea (30.8%), vomiting (19.4%), oral mucositis (34.4%) and hair loss (46.7%).

For the second most relevant variant, rs67376798, González-Perera et al. [13] indicated that this variant was associated with a 30% to 70% decrease in DPYD activity. In the same way, they observed that the patients presented neutropenia, mucositis, and diarrhea. However, to date, none of the detected polymorphisms predict all the severe toxicities seen in patients treated with 5-FU, and their impact on enzyme activity remains to be determined.

The third gene analyzed is Methylene Tetrahydrofolate "MTHFR" reductase, which Levin & Varga [25] has described as a catalyst in the folate metabolism pathway; similarly, Niu et al. [26] mention that this gene irreversibly catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is a cosubstrate in the transmethylation of homocysteine to methionine. Folate plays a crucial role in the formation of S-adenosylmethionine, which is the primary methyl donor during the DNA methylation process, as well as in the formation of purine and thymidine for DNA synthesis. Low levels of 5,10-methylenetetrahydrofolate result in increased amounts of uracil incorporated into DNA to replace thymine, thus increasing the rate of point mutations and resulting in DNA breakage.

In this way, Zhao et al. [27] found that folate deficiency increases the risk of tumorigenesis through one of the following mechanisms: by leading to aberrant DNA methylation, which in turn can lead to altered expression of suppressor genes of critical tumors and proto-oncogenes, or by causing imbalances in nucleotide precursor pools, leading to DNA strand breaks and mutations and impaired DNA integrity and repair.

Levin & Varga [25] indicate that 20 years ago, the existence of two polymorphic variants,

rs1801131 and rs1801133, was discovered, and it was shown that they led to a mild deficiency of the MTHFR enzyme that in turn was related to mild to moderate hyperhomocysteinemia.

Petron et al. [28] report that the rs1801133 variant is associated with a reduced risk of developing carcinoma in high doses of folic acid and vitamins B6, B12, and B2 in subjects with low alcohol intake. However, the risk increases when patients have poor vitamin nutrition.

The study by Thomas et al. [9], including 96 patients treated with 5-FU, reported that the rs1801131 variant was significantly associated with grade 3 diarrhea and mucositis (P = 0.005). Although not significant, the rs1801133 variant was found to protect against grade 3 diarrhea and mucositis in CRC patients.

The last gene analyzed is thymidylate synthase "TYMS"; this gene is the protein encoder and a primary limiting agent that catalyzes the synthesis of pyrimidine nucleotides; studies have shown that its expression level may be related to the efficacy of fluorouracil chemotherapy [29]. According to Castro-Rojas et al. [14], TYMS is the pharmacological target of fluoropyrimidines and is mainly responsible for the cytotoxic effect.

Castro-Rojas et al. [14] carried out a study in a Latin American population, in which they pointed out that TYMS gene variants have predictive values of response and toxicity in patients with CRC treated with chemotherapy based on fluoropyrimidines. In the literature review, two variants, rs45445694 and rs2853542, were analyzed; the first variant predicts severe toxicity and objective response in patients with advanced CRC. Likewise, the authors mention that the second variant is an independent predictor of the failure of the response to chemotherapy.

The study carried out by Abbasian et al. [17], which was conducted on 83 Iranian patients receiving 5-FU-based chemotherapy at Hazrat-Rasool Hospital and Masoud Clinic, Tehran, between February 2014 and June 2016, indicated that the rs45445694 variant is responsible for neurotoxicity in 60% of patients. Ntavatzikos et al. [2,3,30] a conducted a study of 130 early-stage CRC patients from an Attikon General Hospital in Greece, where they determined that TYMS polymorphisms emerged as prognostic factors for survival outcomes in patients treated with surgery and adjuvant chemotherapy. Amirfallah et al. [31] conducted a retrospective study in which eighty-five colorectal cancer patients were treated with fluoropyrimidine-based chemotherapy regimens between 2011 and 2013 at Dokuz University Hospital Eylul in Turkey; in this study, the authors were unable to demonstrate statistically significant associations between TYMS gene polymorphisms and fluoropyrimidine-driven toxicities.

The study's primary endpoint was the frequency with which the variants occur globally and in Latin America 2. In this way, the frequency of the alternative alleles was established as follows:

Table 2. Most frequent alternative alleles. Made by the authors.

gene	Variant	Global Frequency	Variant	Latin American Frequency 2
ABCB1	rs1128503	Guanine = 57.34%	rs1045642	Guanine = 54.80%
DPYD	rs1801265	Guanine = 21.85%	rs1801159	Cytokine = 30.05%
MTHFR	rs1801133	Adenine = 34.01%	rs1801133	Adenine = 45.27%
TYMS	rs45445694	CCGCGCCACTT= 0.00	rs45445694	CCGCGCCACTT= 0.00

Conclusions

In this systematic review, it was possible to collect 11 scientific articles from which information was extracted on 4 genes that encode enzymes involved in the pharmacodynamics and pharmacokinetics of 5-fluorouracil in patients with colorectal cancer: ABCB1 (rs1128503, rs2032592, rs1045642), DPYD (rs3918290, rs22997595, rs1801159, rs1801265, rs17376848, rs67376798, rs55886062), MTHFR (rs1801133, rs1801131) and TYMS (rs45445694), with their respective variants.

The three variants of the ABCB1 gene are related to the presence of neutropenia, diarrhea, hand-foot syndrome, asthenia, and neuropathy; however, the rs1128503 variant is associated with a lower risk of developing colorectal cancer.

The rs3918290, rs55886062, rs67376798, rs1801159, and rs17376848 variants of the DPYD gene were associated with decreased DPYD enzyme activity and a high risk of severe toxicity following 5-fluorouracil administration. The clinical manifestations observed were diarrhea, mucositis, stomatitis, neutropenia, and fatigue. The variables rs22997595 and rs1801265 did not present significant effects.

Within the MTHFR gene, two variants were analyzed: rs1801131 was mainly associated with diarrhea and mucositis, and the rs1801133 variant had a protective effect against diarrhea and mucositis. Finally, in the analysis of the TYMS gene, it was established that the variants rs45445694 and rs2853542 have predictive values of response and toxicity in patients with colorectal cancer treated with 5-FU; these variants are significantly associated with grade 3 neurotoxicity; similarly, the rs45445694 variant was shown to be significantly associated with anemia.

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Abbreviations

DPYD: dihydropyrimidine dehydrogenase
TYMS: thymidylate synthase.

Administrative information

Additional Files

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Author contributions

1. Conceptualization: Cristina Alexandra Benavides Tutillo.
2. Formal analysis: Marí a Gabriela Molina Pinos, Cristina Alexandra Benavides Tutillo.
3. Research: Maritza Raphaela Ochoa Castro, Cristina Alexandra Benavides Tutillo.
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5. Project administration: María Gabriela Molina Pinos.

6. Supervision: María Gabriela Molina Pinos, María Gabriela Molina Pinos
7. Validation: María Gabriela Molina Pinos, Cristina Alexandra Benavides Tutillo.
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10. Writing - revision and editing: Cristina Alexandra Benavides Tutillo, Maritza Raphaela Ochoa Castro.

All authors read and approved the final version of the manuscript.

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Statements

Ethics committee approval

It does not apply to observational studies with a review of databases or medical records.

Consent to publication

This does not apply to studies that do not publish explicit images such as CT scans, MRIs, and physical exam images.

Conflicts of interest

The authors declare that they have no conflict of interest or competence.

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