World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2025 January 15; 17(1): 96822

DOI: 10.4251/wjgo.v17.i1.96822

ISSN 1948-5204 (online)

ORIGINAL ARTICLE

Retrospective Study

Dihydropyrimidine dehydrogenase polymorphisms in patients with gastrointestinal malignancies and their impact on fluoropyrimidine tolerability: Experience from a single Italian institution

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Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade C

Novelty: Grade C, Grade C

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade B, Grade D

P-Reviewer: Yang ZY

Received: May 15, 2024

Revised: August 14, 2024

Accepted: August 28, 2024

Published online: January 15, 2025

Processing time: 210 Days and 14.9 Hours

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Abstract

BACKGROUND

Fluoropyrimidines are metabolized in the liver by the enzyme dihydropyrimidine dehydrogenase (DPD), encoded by the *DPYD* gene. About 7% of the European population is a carrier of *DPYD* gene polymorphisms associated with reduced DPD enzyme activity.

AIM

To assess the prevalence of *DPYD* polymorphisms and their impact on fluoropyrimidine tolerability in Italian patients with gastrointestinal malignancies.

METHODS

A total of 300 consecutive patients with a diagnosis of gastrointestinal malignancy and treated with a fluoropyrimidine-based regimen were included in the analysis and divided into two cohorts: (1) 149 patients who started fluoropyrimidines after *DPYD* testing; and (2) 151 patients treated without *DPYD* testing. Among the patients in cohort A, 15% tested only the *DPYD2A* polymorphism, 19% tested four polymorphisms (*DPYD*2A, HapB3, c.2846A>T, and *DPYD*13), and 66% tested five polymorphisms including *DPYD*6.

RESULTS

Overall, 14.8% of patients were found to be carriers of a *DPYD* variant, the most common being *DPYD*6 (12.1%). Patients in cohort A reported ≥ G3 toxicities (P = 0.00098), particularly fewer nonhematological toxicities (P = 0.0028) compared with cohort B, whereas there was no statistically significant difference between the two cohorts in hematological toxicities (P = 0.6944). Significantly fewer che-

motherapy dose reductions (P = 0.00002) were observed in cohort A compared to cohort B, whereas there was no statistically significant differences in chemotherapy delay.

CONCLUSION

Although this study had a limited sample size, it provides additional information on the prevalence of *DPYD* polymorphisms in the Italian population and highlights the role of pharmacogenetic testing to prevent severe toxicity.

Key Words: Dihydropyrimidine dehydrogenase; *DPYD* polymorphisms; Fluoropyrimidine; Caucasian population; Gastrointestinal cancers

Core Tip: In this retrospective study, we report the prevalence of *DPYD* polymorphisms in a real-world population of patients treated for gastrointestinal malignancies and their impact on fluoropyrimidine tolerability. Furthermore, we demonstrate that the presence of polymorphisms in the *DPYD* gene, which encodes dihydropyrimidine dehydrogenase, leads to an increased risk of G3/G4 nonhematologic toxicity and more frequent dose reductions. We did not find a significant difference in chemotherapy delay.

Citation: D'Amato M, Iengo G, Massa N, Carlomagno C. Dihydropyrimidine dehydrogenase polymorphisms in patients with gastrointestinal malignancies and their impact on fluoropyrimidine tolerability: Experience from a single Italian institution. *World J Gastrointest Oncol* 2025; 17(1): 96822

URL: https://www.wjgnet.com/1948-5204/full/v17/i1/96822.htm

DOI: https://dx.doi.org/10.4251/wjgo.v17.i1.96822

INTRODUCTION

5-Fluorouracil (5-FU) was introduced into clinical practice about 60 years ago[1], and still represents the backbone of therapy for early and metastatic gastrointestinal tumors. Furthermore, its oral prodrug (capecitabine) is widely used for the treatment of gastrointestinal, breast, and head and neck cancers[2]. After intravenous administration, 5-FU is converted to fluorodeoxyuridine monophosphate, which binds and inhibits thymidylate synthase, resulting in reduced DNA and RNA synthesis[3]. After rapid intestinal absorption, the oral 5-FU prodrug, capecitabine, is converted in the liver to 5'-deoxy-5-fluorocytidine, which is transformed to 5'-deoxy-5-fluorouridine and finally converted to 5-FU[4]. 5-FU is metabolized in the liver by the enzyme dihydropyrimidine dehydrogenase (DPD) encoded by the gene *DPYD*, which has several polymorphisms, some of which cause decreased enzyme activity[5]. The ability to eliminate fluoropyrimidines can be assessed at different time points, from the gene encoding the DPD enzyme to the 5-FU catabolic pathway (different ways to analyze fluoropyrimidine metabolism): (1) The detection of relevant *DPYD* gene single nucleotide polymorphisms; (2) The level of *DPYD* mRNA expression; (3) The evaluation of DPD activity in peripheral blood mononuclear cells with radioenzymatic techniques; (4) The measurement of uracil, a natural substrate of DPD, in plasma or urine; (5) The uracil ratio in plasma, *i.e.* the ratio of catabolite (dihydrouracil) to substrate (uracil) of DPD; and (6) The more recent (2-C13) uracil breath test[6,7].

The most commonly used method is the evaluation of polymorphisms of the *DPYD* gene due to large availability, affordable costs, and well-defined risk and dose adjustments for variant carriers[6]. The most studied *DPYD* variants associated with reduced DPD activity are c.1905+1G>A (rs3918290, *DPYD*2A), c.1679T>G (rs55886062, *DPYD*13), c.2846A>T (rs67376798, p.D949V), and c.1129–5923C>G (rs75017182, HapB3)[8]. Furthermore, other variants such as c.2194G>A (rs1801160, *DPYD*6) are associated with moderate reductions of the enzyme activity[9]. Hematological toxicity, nausea, vomiting, diarrhea, mucositis, and hand-foot syndrome are the most common adverse events associated with fluoropyrimidines[10] and polymorphisms that cause reduced DPD activity may increase these toxicities[8,11]. Two prospective studies have shown that adjusting the dose of fluoropyrimidines based on the presence of *DPYD* variants can significantly reduce the incidence of serious toxicities and deaths, as well as save costs of adverse event management[12,13]. In 2020, the European Medicines Agency (EMA) recommended that DPD activity be assessed before the administration of 5-FU, capecitabine, or tegafur, an oral prodrug of 5-FU used primarily in Asia. Soon afterwards, the Associazione Italiana di Oncologia Medica (AIOM) recommended *DPYD* polymorphisms testing before systemic fluoropyrimidine therapy initiation, and a dose reduction if variants are detected. According to the Clinical Pharmacogenetics Implementation Consortium, approximately 7% of the European population carries at least one variant conferring reduced DPD activity, and the most common polymorphism is *DPYD*-HapB3[14]. In Italy, several papers have reported the results of *DPYD* variants testing in selected populations, mainly in clinical trials, but data on the real-world prevalence of the *DPYD* polymorphism are still limited.

The aim of the present study was to evaluate the prevalence of the most common *DPYD* polymorphisms in patients treated with 5-FU or capecitabine (alone or in combination with radiotherapy or other drugs) for gastrointestinal cancer at our institution. We also assessed the association between *DPYD* testing and grade 3 or higher adverse events, dose reductions, and treatment delays.

MATERIALS AND METHODS

This retrospective analysis included 300 patients, older than 18 years, Caucasian race, who were consecutively referred at our Institution from January 2016 to July 2023. Patients should have a histological diagnosis of a gastrointestinal malignancy, requiring chemotherapy with a fluoropyrimidine-based regimen (5-FU or capecitabine), either as monotherapy or in combination with radiotherapy or other agents. The whole population was divided into two cohorts: Cohort A, including patients treated after *DPYD* testing; and cohort B, including patients treated without *DPYD* testing. *DPYD* assessment was performed in several accredited laboratories in our region, according to the patient's residence. The initial dose of fluoropyrimidine was calculated according to the patient's body surface, and reductions were applied based on age, comorbidities, and renal function, which was estimated by the creatinine clearance calculated using the Cockcroft-Gault formula[15]. In case of the presence of a *DPYD* polymorphism, the appropriate dose of fluoropyrimidine was calculated according to the AIOM recommendations. Descriptive statistics were used to show the demographic and clinical characteristics of the study population and the prevalence of the *DPYD* gene polymorphism in patients in cohort A. Hematological and non-hematological adverse events were assessed after each cycle of chemotherapy and graduated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4. We estimated the correlation between pharmacogenetic testing and toxicity by comparing the occurrence of grade ≥ 3 adverse events in cohort A and cohort B using the χ^2 test (or Fisher's exact test, if necessary), with α error defined as 0.05.

RESULTS

Three hundred consecutive patients treated at our institution from January 2016 to July 2023 were enrolled (Table 1). Cohort A included 149 patients, treated after publication of the EMA recommendations for *DPYD* testing. Cohort B included 151 patients, treated without *DPYD* testing, before EMA recommendations. Levene's test was applied to evaluate the variability between cohorts A and B, obtaining $P > 0.05$ (0.58371), confirming that the patients' characteristics were well-balanced between the two cohorts (Table 1). About half of the patients were male (165/300, 55%); most patients had large bowel tumors, 55.7% colon, and 26% had rectal adenocarcinoma. About two-thirds of the patients had an early-stage neoplasm with a slightly higher prevalence in cohort A (70%) compared to cohort B (63%). Overall, the number of patients with metastatic disease was 45 (30%) in cohort A and 56 (37%) in cohort B, with 35 (23.5%) and 43 (28.5%) patients with liver metastases in cohorts A and B, respectively. None of the patients with liver metastases had liver impairment greater than grade 1. Fluoropyrimidines were administered as monotherapy in 14% of cases, in combination with radiotherapy in 18%, and doublet with another chemotherapeutic agent in 61.7% of the patients. Patients who received chemoradiotherapy were 20 of 149 in cohort A, and 34 of 151 in cohort B. However, only 1 patient in cohort B received doublet chemotherapy in combination with radiotherapy, in contrast to cohort A in which 7 patients received doublet chemotherapy in combination with radiotherapy. All patients in cohort A were tested for *DPYD*2A (c.1905+1G>A) polymorphism; 23/149 (15%) patients were only tested for *DPYD*2A, 28/149 (19%) patients were tested for the four main polymorphisms (*DPYD*2A, *DPYD*13, HapB3, c.2846A>T), and 98/149 (66%) patients were tested for *DPYD*6 in addition to the four main polymorphisms (Figure 1). *DPYD* testing was performed in various accredited external laboratories, which has progressively implemented this analysis after publication of the EMA and AIOM recommendations[13,14], thereby explaining the variability in the number of polymorphisms analyzed, ranging from a minimum of one polymorphism to a maximum of five polymorphisms. In cohort A, 127/149 patients (85.2%) were wild-type, 2/149 (1.3%) were heterozygous for HapB3 variant, 1/149 (0.7%) was heterozygous for *DPYD*2A, 1/149 (0.7%) was heterozygous for c.28496A>T, 17/149 (11.4%) were heterozygous for *DPYD*6, and 1/149 (0.7%) was homozygous for *DPYD*6 (Table 2). The prevalence of the four main variants was 2.7%, while it raised to 14.8% if *DPYD*6 was considered. The most detected variant was *DPYD*6, followed by HapB3, whereas no *DPYD*13 variant was found. Table 3 summarizes the worst toxicity reported during the treatment. Overall, 39/149 patients in cohort A (26.17%) and 67/151 in cohort B (44.37%) had at least one grade 3 or higher (≥ G3) adverse event, with a statistically significant difference between the two cohorts ($P = 0.00098$). Hematologic toxicities had a similar incidence in both cohorts: 26/149 (17.4%) patients in cohort A and 29/151 (19.2%) patients in cohort B. Non-hematologic toxicities were much more common in cohort B, 20/151 (13.2%), compared to cohort A, 5/149 (3.4%). In total, 33/149 patients in cohort A (22.15%) and 69/151 in cohort B (45.7%) required fluoropyrimidine dose reduction, with a statistically significant difference ($P = 0.00002$). In cohort B, the main cause for dose reductions during treatment was G ≥ 3 non-hematologic toxicity (42/151 [27.8%]), while 16/151 (10.6%) patients had grade 3 or higher hematologic toxicities. In cohort A, the dose was reduced because of hematologic toxicities in 17/149 (11.4%) patients and the same was for non-hematologic toxicities. At least one cycle of chemotherapy was delayed in 38/149 (25.5%) patients in cohort A and 52/151 (34.44%) in cohort B, with a non-statistically significant difference ($P = 0.09136$). Chemotherapy cycles were delayed for toxicities of any grade, predominantly for hematologic ones in both cohorts. Specifically, in cohort A, 29/149 (19.5%) patients required chemotherapy delay because of hematologic toxicities, 8/149 (5.4%) for non-hematologic toxicities, and 8/149 (5.4%) for both types of toxicities. In cohort B, 22/151 (14.6%) patients required chemotherapy delay due to hematologic toxicity, 20/151 (13.2%) due to non-

Table 1 Demographic and clinical characteristics

Characteristic	*DPYD* testing, *n* = 149	No *DPYD* testing, *n* = 151	Total, *n* = 300
Median age	66 (84-33)	65 (85-34)	65 (85-33)
ECOG PS			
0	133 (89)	143 (95)	276 (92)
1	16 (11)	8 (5)	24 (8)
Sex			
Male	79 (53)	86 (57)	165 (55)
Female	70 (47)	65 (43)	135 (45)
Type of cancer			
Colon	80 (54)	87 (58)	167 (55.7)
Rectal	32 (21)	46 (30)	78 (26)
Gastric	29 (19)	16 (11)	45 (15)
Esophageal	1 (1)	0 (0)	1 (0.3)
Anal	7 (5)	1 (1)	8 (2.7)
Appendiceal	0 (0)	1 (1)	1 (0.3)
Stage of disease			
Localized	104 (70)	95 (63)	199 (66.3)
Metastatic	45 (30)	56 (37)	101 (33.7)
Type of treatment			
Monotherapy	23 (15)	20 (13)	43 (14)
Monotherapy + RT	20 (13)	34 (23)	54 (18)
Doublet	97 (65)	88 (58)	185 (61.7)
Triplet	9 (6)	9 (6)	18 (6)

Data are *n* (%). ECOG: Eastern cooperative oncology group; PS: Performance Status; RT: Radiotherapy.

Table 2 Prevalence of *DPYD* polymorphisms

DPYD variant	Number detected (%)
HapB3	2 (1.3)[1]
*DPYD*2A	1 (0.7)[1]
c.2846A>T	1 (0.7)[1]
*DPYD*13	0 (0)
*DPYD*6	18 (12.1)[2]
Wild-type	127 (85.2)
All polymorphisms	22 (14.8)
All polymorphisms except *DPYD*6	4 (2.7)

[1]All in heterozygosity.
[2]All in heterozygosity except 1 in homozygosity.
Data are *n* (%).

Table 3 Correlation between *DPYD* polymorphisms and toxicity

Parameter	Cohort A, *n* = 149	Cohort B, *n* = 151	*P* value
Patients with any AEs ≥ G3	39 (26.17)	67 (44.37)	0.00098
Patients with FP dose reduction	33 (22.15)	69 (45.7)	0.00002
Patients with ChT delay for any grade AEs	38 (25.5)	52 (34.44)	0.09136
Patients with hematological AEs ≥ G3	26 (17.4)	29 (19.3)	0.6944
Patients with non-hematological AEs ≥ G3	5 (3.4)	20 (13.3)	0.0028

Data are *n* (%). AEs: Adverse events; ChT: Chemotherapy; FP: Fluoropyrimidine.

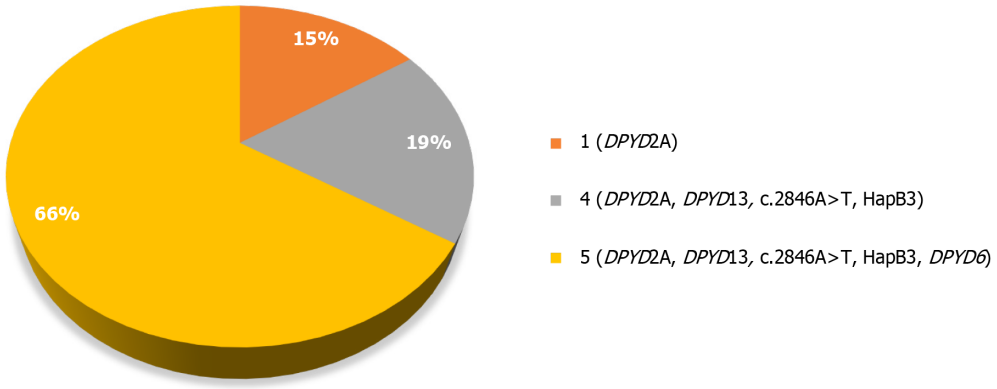

Figure 1 Polymorphisms analyzed.

hematologic toxicity, and 4/151 (2.6%) due to both types of toxicity. In cohort A, 17/149 (11.4%) patients required chemotherapy delay due to at least grade 3 hematologic toxicity, and 2/149 (1.3%) due to at least grade 3 non-hematologic toxicity. In cohort B, 3/151 (2%) patients had chemotherapy delay due to both hematologic and non-hematologic toxicity, 21/151 (13.9%) due to hematologic toxicity, and 5/151 (2%) due to non-hematologic toxicity. In some cases, toxicities of any grade resulted in a reduction in fluoropyrimidine dose without chemotherapy delay need, as they recovered or improved to a lower grade by the end of the cycle. Specifically, 19/149 (12.8%) patients in cohort A and 27/151 (17.9%) patients in cohort B received dose reduction due to non-hematologic toxicities without the need to delay chemotherapy. In total, 1/149 (0.7%) patient in cohort A and 1/151 (0.7%) patient in cohort B received dose reduction due to hematologic toxicities, with no need to delay chemotherapy; and 1/149 (0.7%) patient in cohort A and 5/151 (3.3%) patients in cohort B received dose reduction without chemotherapy delay for both hematologic and non-hematologic toxicities.

DISCUSSION

EMA recommendations raised awareness about the benefits of pharmacogenetic testing among oncologists and national health services. The survey by de With *et al*[16] showed that in Europe, before 2020, *DPYD* testing was difficult to perform routinely, due to a lack of reimbursability, lack of knowledge of the clinical relevance of the test, and lack of clear and unambiguous guidelines. In Italy, there was a progressive increase in the analysis of *DPYD* polymorphisms following the publication of EMA and AIOM recommendations and reimbursement of the test by the National Health Service. Thus, the laboratories progressively implemented the number of polymorphisms tested, from one (*DPYD*2A) to five (*DPYD*2A, HapB3, c.2846A>T, *DPYD*13, *DPYD*6). This is the reason why in our study, 23/149 (15%) patients were tested for only one polymorphism, *DPYD*2A, which was the first polymorphism to be investigated and whose relevance in clinical practice is known[12]. In our study population, the prevalence of the four most common variants of the *DPYD* gene, namely, *DPYD*2A (c.1905+1G>A), c.2846A>T, *DPYD*13 (c.1679T>G), and c.1236G>A/HapB3, was 2.7%. These data were consistent with those reported in several studies including European populations (Table 4): 4.8% in Spain[17], 7.5% in Denmark[18], 4.65% in France[19], and 8% in Netherlands[13]. To the best of our knowledge, few data are available on the prevalence of *DPYD* gene polymorphisms in the Italian real-world population, as most information is derived from retrospective analyses of patients with gastrointestinal cancers enrolled in clinical trials. The most representative series are those recruited for the TOSCA Phase 3 trial (randomized trial investigating the role of oxaliplatin, fluorouracil and leucovorin calcium-4 regimen duration [3 months *vs* 6 months] and bevacizumab as adjuvant therapy for patients with stage 2/3 colon cancer) and the TRIBE Phase 3 trial (randomized trial of oxaliplatin, irinotecan, fluorouracil, and

Table 4 Prevalence of *DPYD* polymorphisms in European populations

Polymorphism	Photo *DPYD* Spain[17], *n* = 8054	Paulsen Denmark[18], *n* = 4215	Pallet France[19], *n* = 3680	Henricks Netherland[13], *n* = 1103
*DPYD*2A	55 (0.7)	43 (1)	25 (0.67)	16 (1)
*DPYD*13	15 (0.2)	8 (0.2)	4 (0.1)	1 (< 1)
Hap3B	209 (2.6)	208 (4.9)	109 (2.96)	51 (5)
c.2846A>T	105 (1.3)	57 (1.4)	34 (0.92)	17 (2)
Total	384 (4.8)	316 (7.5)	172 (4.65)	85 (8)

Data are *n* (%).

leucovorin calcium + bevacizumab *vs* irinotecan, fluorouracil, and leucovorin calcium + bevacizumab as first-line treatment for metastatic colorectal cancer) and a single institution population analysis (Table 5). In the ancillary pharmacogenetic analysis of the TOSCA trial, which enrolled patients candidate to adjuvant chemotherapy after radical resection of high-risk stage 2/3 colon cancer, a total of 10 *DPYD* variants were retrospectively analyzed. Considering only the four variants recommended by the AIOM guidelines (c.1905+1G>A [rs3918290, *DPYD*2A], c.1679T>G [rs55886062, *DPYD*13], c.2846A>T [rs67376798, p.D949V], and c.1129–5923C>G [rs75017182, HapB3]), 19/508 (3.7%) patients were carriers of a variant in heterozygosity, while 5/508 (1%) patients were carriers of a variant in homozygosity. When the c.2194G>A (rs1801160, *DPYD*6) polymorphism was also included, a total of 84/508 (16.5%) patients were found to be carriers of at least one variant in heterozygosity[20]. In the TRIBE trial, which enrolled patients with metastatic colorectal cancer for first-line treatment, only the three *DPYD* variants mostly affecting DPD activity were tested (c.1905+1G>A [rs3918290, *DPYD*2A], c.2846A>T [rs67376798, p.D949V], and c.1679T>G [rs55886062, *DPYD*13]), and 10/439 (2.3%) patients resulted in heterozygous carriers, 5/439 (1.1%) of the c.2846A>T variant and 5/439 (1.1%) of the *DPYD*2A variant, respectively. No carrier of *DPYD* c.1679T>G (rs55886062, *DPYD*13) was identified, as it occurred in our series[21]. In a single Italian institution analysis, five polymorphisms were tested in 1000 patients with gastrointestinal malignancies, candidates for fluoropyrimidines. The variants tested were those recommended by AIOM (c.1905+1G>A [rs3918290, *DPYD*2A], c.1679T>G [rs55886062, *DPYD*13], c.2846A>T [rs67376798, p.D949V], and c.1129–5923C>G [rs75017182, HapB3]), plus c.2194G>A (rs1801160, *DPYD*6). When only four polymorphisms were considered, 39/1000 (3.9%) patients were carriers of a variant in heterozygosity, while no carriers of a variant in homozygosity were found. If all five polymorphisms were included, 180/1000 (18%) patients were heterozygous carriers, and 5/1000 (0.5%) patients resulted in homozygous carriers of the *DPYD*6 variant[22]. Overall, the results of our series are very consistent with those of the other Italian study, confirming that the evaluation of the *DPYD* gene polymorphism is very a reproducible and reliable analysis when performed by quality controlled laboratories. Regarding toxicity, the present study confirmed the role of *DPYD* testing in reducing the risk of developing serious adverse events, as we observed a statistically significant difference in terms of ≥ G3 toxicity and the occurrence of chemotherapy dose reduction between cohort A (*DPYD* test) and cohort B (no *DPYD* test). In our series, patients who started fluoropyrimidine-based therapy after *DPYD* testing experienced less severe toxicity (particularly, less hand-foot syndrome and mucositis) and required fewer dosage adjustments during treatment. There was no statistically significant difference in the delay of therapy due to toxicity between the two cohorts, even though the number of delays was numerically greater in the untested group. A possible explanation for the occurrence of dose reduction without treatment delay is that many severe toxicities in cohort B resolved by the end of the cycle without causing a chemotherapy delay. In addition, the chemotherapy delay was also due to less than grade 3 toxicities. TOSCA and TRIBE retrospective analyses also evaluated the association between the presence of *DPYD* variants and the occurrence of severe toxicity, with similar results. In the TOSCA trial, a statistically significant association was found between the presence of the c.2194G>A (rs1801160, *DPYD*6) polymorphism and the development of severe toxicities[20]. Furthermore, the variants rs181160, rs2297595, and rs3918290 were also correlated to a shorter time-to-toxicity, underlining not only the occurrence of severe adverse events but also the shorter time to toxicity onset in patients carrying *DPYD* polymorphisms[20]. In the TRIBE study, 8 of the 10 patients with polymorphisms (80%) developed at least one ≥ G3 toxicity, mainly neutropenia and stomatitis[21]. In conclusion, the present study, although conducted with a limited sample size, provides additional information about the prevalence of *DPYD* gene polymorphisms in the Italian population and confirms the importance of performing pharmacogenetic testing to prevent severe fluoropyrimidine toxicities. Studies with larger sample sizes may provide more accurate data on the prevalence of the different polymorphisms in the different populations and more accurate information on the role of each *DPYD* variant on the fluoropyrimidine-induced toxicity, to better tailor the *DPYD* testing before fluoropyrimidine treatment in the Italian patients.

CONCLUSION

Although the sample size was limited and the analysis was retrospective, this analysis provides additional information on the prevalence of *DPYD* polymorphisms in the Italian population. Furthermore, this analysis highlights the role of

Table 5 *DPYD* polymorphisms analysis in Italian cancer patients

Feature	TOSCA trial[20]	TRIBE trial[21]	IRCCS Pascale[22]
Setting	Colon cancer high-risk stage 2 or stage 3	Colo-rectal cancer stage 4	Gastrointestinal malignancies
Treatment	FOLFOX/CAPOX	FOLFOXIRI/FOLFIRI + bevacizumab	Patients candidates for fluoropyrimidines
Patients	508	439	1000
Total number of tested variants	10	3	5
Prevalence of the four recommended variants in heterozygosity	19/508 (3.7)	10/439 (2.3)[1]	39/1000 (3.9)
Prevalence of the four recommended variants + *DPYD*6 in heterozygosity	84/508 (16.5)	0/439 (0)[2]	180/1000 (18)
Prevalence of the four recommended variants + *DPYD*6 in homozygosity	5/508 (1.0)[3]	0/439 (0)[2]	5/1000 (0.5)[3]

[1]HapB3 not analyzed.
[2]HapB3 and *DPYD*6 not analyzed.
[3]All *DPYD*6.
Data are *n* (%). TOSCA: A randomized trial investigating the role of oxaliplatin, fluorouracil and leucovorin calcium-4 regimen duration (3 months *vs* 6 months) and bevacizumab as adjuvant therapy for patients with stage 2/3 colon cancer; TRIBE: Phase 3 randomized trial of oxaliplatin, irinotecan, fluorouracil, and leucovorin calcium + bevacizumab *vs* irinotecan, fluorouracil, and leucovorin calcium + bevacizumab as first-line treatment for metastatic colorectal cancer. CAPOX: Capecitabine and oxaliplatin; FOLFIRI: Irinotecan, fluorouracil, and leucovorin calcium; FOLFOX: Oxaliplatin, fluorouracil, and leucovorin calcium; FOLFOXIRI: Oxaliplatin, irinotecan, fluorouracil, and leucovorin calcium; IRCCS: Scientific institute for research, hospitalization and healthcare.

pharmacogenetic testing before treatment with fluoropyrimidines to prevent severe toxicity.

FOOTNOTES

Author contributions: D'Amato M and Carlomagno C participated in the conception and design of the study, analyzed the data, and wrote the original manuscript; D'Amato M collected the data; D'Amato M, Iengo G, Massa N, and Carlomagno C critically reviewed and provided final approval of the manuscript; D'Amato M, Iengo G, Massa N, and Carlomagno C were responsible for the decision to submit the manuscript for publication.

Institutional review board statement: The investigation was approved by the panel of scientists proposing the research and by all the collaborators who participated in the research.

Informed consent statement: The need for patient consent was waived due to the retrospective nature of the study.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: No additional data are available.

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S-Editor: Fan M
L-Editor: Filipodia
P-Editor: Zhang L

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