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Relationship Between Dihydropyrimidine Dehydrogenase Gene Polymorphism and Toxicities in Cancer Patients Receiving 5-Fluorouracil

5-Florourasil Alan Kanser Hastalarında Dihidropirimidin Dehidrojenaz Gen Polimorfizmi ile Toksisiteler Arasındaki İlişki

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ABSTRACT

Objective: Dihydropyrimidine dehydrogenase (DPD) is a rate-limiting enzyme that degrades uracil, thymine, and 5-fluorouracil, which are important for treating gastric, colorectal, and breast cancers. In this study, we aimed to determine the association between chemotherapy-related toxicities and DPD gene variants; evaluate the consequences of these genetic differences; and integrate DPYD genetic screening into conventional cancer treatment regimens.

Methods: Sixty-two patient files from 2015 to 2018 were retrospectively reviewed to investigate whether the DPYD gene causes toxicity before or during treatment. A total of 50 patients were enrolled after receiving informed consent and ethical clearance for the comprehensive examinations. The aim of this study was to reveal the genetic causes of adverse effects and better understand treatment responses.

Results: Our analysis of 50 patients with cancer revealed that the severity of response to fluoropyrimidine compounds used in chemotherapy varied depending on DPYD gene polymorphisms. These mutations increased susceptibility to severe neutropenia -which can weaken immune systems- among other negative effects. It also found that IVS14 + 1G>A had a significant effect on treatment outcome, indicating that genetic screening should be included in planning therapy as it can prevent major side effects.

Conclusion: Dihydropyrimidine connected to dehydrogenase gene polymorphism occurred in patients with gastrointestinal cancer who developed diarrhea, nausea, anemia, thrombostitopenia, and grade 3-4 neutropenia side effects while receiving 5-FU.

Keywords: Dihydropyrimidine dehydrogenase, 5-fluorouracil, gene polymorphism

ÖZ

Amaç: DPD (dihydropyrimidine dehydrogenase), mide, kolorektal ve meme kanserlerinin tedavisinde urasil, timin ve 5-florourasili parçalayan hız sınırlayıcı bir enzimdir. Bu çalışmada kemoterapiye bağlı toksisiteler ile DPD gen varyantları arasındaki ilişkiyi belirlemeyi, bu genetik farklılıkların sonuçlarını değerlendirmeyi ve DPYD genetik taramasını geleneksel kanser tedavi rejimlerine entegre etmeyi amaçladık.

Yöntem: DPYD geninin tedavi öncesi veya tedavi sırasında toksisiteye neden olup olmadığını araştırmak için 2015'ten 2018'e kadar altmış iki hasta dosyası geriye dönük olarak gözden geçirildi. Kapsamlı muayeneler için bilgilendirilmiş onam ve etik izin alındıktan sonra toplam 50 hasta alındı. Amaç, yan etkilerin genetik nedenlerini ortaya çıkarmak ve tedavi yanıtlarını daha iyi anlamaktır.

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Bulgular: Elli kanser hastası üzerinde yaptığımız analiz, kemoterapide kullanılan floropirimidin bileşiklerine yanıt şiddetinin DPYD gen polimorfizmlerine bağlı olarak değiştiğini ortaya koydu. Bu mutasyonlar, diğer olumsuz etkilerin yanı sıra bağışıklık sistemlerini zayıflatabilen şiddetli nötropeniye duyarlılığı artırdı. Ayrıca IVS14 + 1G>A'nın, majör yan etkileri önleyebileceği için genetik taramanın planlama tedavisine dahil edilmesi gerektiğini gösteren yönetim üzerinde önemli bir etkisi olduğunu bulduk.

Sonuç: Dehidrojenaz gen polimorfizmine bağlı dihidropirimidin, 5-FU ile tedavi edilirken ishal, bulantı, anemi, tyrostitopeni, nötropeni grade 3-4 yan etkileri gelişen gastrointestinal kanser olgularında ortaya çıkmıştır.

Anahtar Kelimeler: Dihidropirimidin dehidrojenaz, 5-florourasil, gen polimorfizmi

INTRODUCTION

Dihydropyrimidine dehydrogenase (DPD) (EC 1.3.1.2) is a rate-limiting enzyme that degrades uracil, thymine, and 5-fluorouracil.[1] Intracellular 5-FU phosphorylation and activation inhibit DNA synthesis and RNA dysfunction.[2] In 10-30% of patients, an important treatment for gastric, colorectal, and breast malignancies causes significant side effects, such as neutropenia, thrombocytopenia, mucositis, diarrhea, and hand-foot syndrome.[3] A DPD-mediated three-step metabolic process excretes more than 80% of 5-FU.[4] DP puts the first step by converting 5-FU to dihydro-5-FU. DHP (EC 3.5.2.2) hydrolyzes FUH2, which is then converted into fluoro-β-alanine after β-ureidopropionase (β-UP, EC 3.5.1.6) converts fluoro-β-ureidopropionic acid created in the previous steps.[5] A severe 5-FU poisoning can be caused by any of these enzymes, but DPD, the rate-limiting enzyme, is most important.[5] Due to 5-FU accumulation and blood levels, DPD deficiency can increase antitumor effects or toxicity.[6]

DPD is expressed by more cells, but liver and lymphocytes seem to be more active.[7] DPYD, which is on chromosome 1p21 has an open reading frame of 3,078 bp and 1,025 amino acid residues.[8] It is made up of 23 exons. Amino acid sequences and enzymatic activities can be modified by DPYD SNVs, deletions and insertions. Clinical symptoms such as seizures, mental illness, microcephaly, autism in sick people and asymptomatic people in DPD deficiency.[9,10] Microdeletion and chromosomal instability in the 1p21 region of DPYD also lead to this autosomal recessive genetic disorder. DPD deficit can only be detected after 5-FU treatment, which causes significant toxicity in asymptomatic individuals; thus, predicting the toxicity risk is vital. In addition to four Caucasian risk variants of DPYD: C.1905+1G>A (IVS14+1G>A, DPYD*2A), C.1129-5923C>G/hapB3, C.1679T>G (DPYD*13, p. I560S), and C.2846A>T, there have been more than 450 variations of the gene.[11,12] Splicing mistakes or amino-acid alterations affect the enzymatic activity.[13,14] The Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group recommend modifying 5-FU doses for DPYD genetic variations.[15]

Our research shows that comprehensive studies are rare that could help prove the clinical benefits of DPYD polymorphism screening as part of cancer treatment planning. Although current studies have provided a basic understanding of the correlation between DPD variants and chemotherapy toxicity; no consensus has been reached regarding the effects of these genetic tests on treatment outcomes and patient management strategies. To enable personalized medicine approaches in oncology, we need to further investigate the prevalence of DPYD polymorphisms among different populations and cancer types and their effects on toxicity profiles.

However, this study sets out to clarify the situation by examining chemotherapy toxicity resulting from a mix of certain Dec gene polymorphisms in patients. The overall goal is to determine whether it is worth integrating genetic tests into routine cancer treatment protocols. This will increase the effectiveness of treatments, reduce negative effects, and improve the overall quality of life of patients with cancer.

METHODS

The study was approved by the Ethical Review Board of Harran University Faculty of Medicine, Şanlıurfa (approval number: E13607, date: 25.03.2019). From January 1st 2015 through January 1st 2018 at our University Faculty of Medicine Research and Application Hospital Department of Medical Oncology were examined as part of a preliminary trial (62 patient files). Evaluation for inclusion in the study was given regardless of whether the patient was admitted as a hospitalized or outpatient but had to be set up for chemotherapy. With approval from the ethics committee and after informed consent was obtained from each patient, the boundaries were determined so that only those who could reliably report chemotherapy symptoms and the effects of DPYD gene polymorphism on treatment outcomes (Figure 1), which included 50 patients after removing untraceability (n=2), prestudy death (n=3) and inadequate data records (n=7) (Figure 1).

Patients were informed of the study design and its objective. The study was approved by the Ethical Review Board of Harran University Faculty of Medicine, Şanlıurfa (approval number: E13607, date: 25.03.2019), in accordance with national patient care guidelines, and met international ethical standards for research involving humans. Patients

received full disclosure of the tests that would be performed on them and any potential side effects caused by these tests. Before and 10 days after chemotherapy, patients underwent complete blood counts and biochemical testing to evaluate their baseline health status and detect any changes. Just before treatment, a blood sample was collected from each patient for genetic polymorphism analysis, especially for DPYD gene polymorphisms, and kept at -80 ºC until DNA extraction followed by real-time polymerase chain reaction (PCR) analysis.

To analyze the association between genetic polymorphism (DPYD * 2A, * 13, *9B) and toxicity during two periods: pre-chemotherapy assessment 10 days before chemotherapy; post-chemotherapy assessment 10 days after chemotherapy to identify genetic factors responsible for adverse reactions to drugs currently used in clinical practice (chemotherapies) as well as those used separately or associated with other drugs in individual patients; detailed protocols were used according to manufacturer instructions to extract blood DNA from each patient. After homogenization for at least 2 h at room temperature together with the addition of QIAGEN protease to the buffer AL + ethanol mixture (spin column), centrifugation

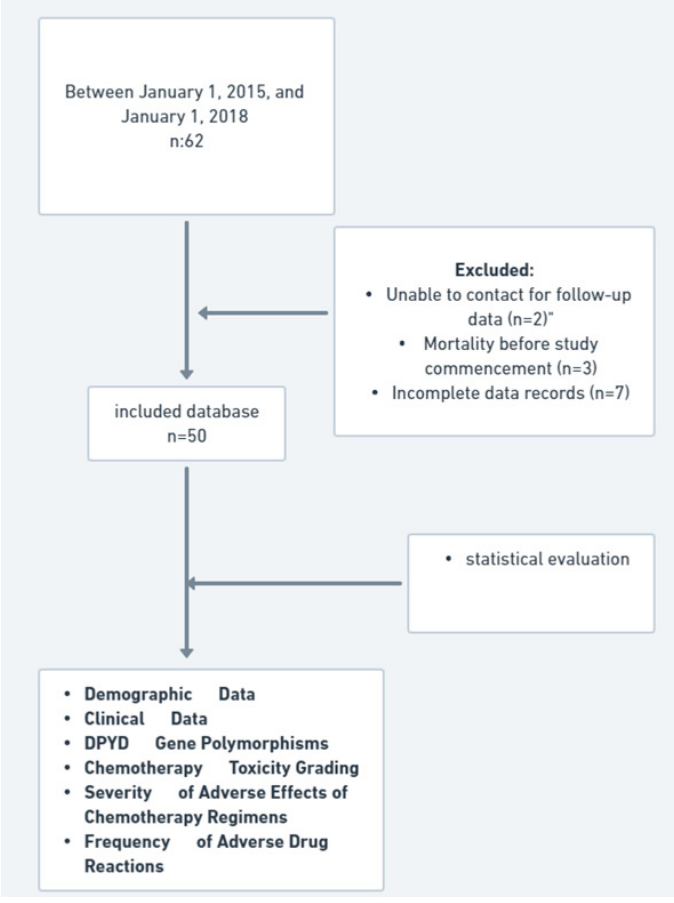

Figure 1. Study design

occurred. Polymorphism screening needs high-quality DNA-which was what our protocol provided. DPYD gene variants were detected using a Taqman Genotyping Assay and Master Mix polymorphism screening using qPCR.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences for Windows version 20.0; continuous variables are presented as mean±standard deviation; categorical variables are presented as frequency (%) or number (%); parametric variables were compared using Student's t-test or Mann-Whitney U test; categorical variables were compared using chi-square test or Fisher's exact test. P values <0.05 were considered statistically significant.

RESULTS

We collected and analyzed the medical records of 50 patients, including personal data such as age, sex, anthropometric measurements, tumor type, cancer staging, and chemotherapy treatment regimens. The sample consisted of 27 men (54%) and 23 women (46%), with a mean age of 54.18±14.40 years; the prevalence rate reflects that cancer is more common in women than in men: breast cancer was the most frequent among women, while prostate cancer was the most frequent among men; The mean weight was 66.88 kg (±15.47 kg), and the mean height was 164.50 cm (±7.22 cm), reflecting the fact that each patient had their own health condition; cancer stages ranged from 2 to 4: Stage 2 corresponded to 20% of the sample, Stage 2 corresponded to 25%, Stage 3 corresponded to another third (30%), and Stage 4 corresponded to another quarter (25%), highlighting that although all have cancer - it doesn't always mean they have the same stage - making it even more important to personalize treatments in order to obtain better results by reducing possible side effects associated with them; chemotherapy regimens included FEC, FOLFOX, and cisplatin-based treatments tailored according to tumor type and stage. We have now included a detailed analysis of the side effects according to the chemotherapy regimens to enhance the understanding and management of patient care (Table 1).

Our analysis using genotyping showed higher rates of DPYD gene variant detection than expected for variants DPYD *2A rs3918290 c.-166G>T rs55886062 c.-96T>G rs67376798 c.-1103C>G HapB3c.-1601C>A. These results are meaningful because these polymorphisms are associated with severe reactions to fluoropyrimidine, which are widely used in chemotherapy. In the future, it will be necessary to screen and identify people at risk of adverse responses and reduce the dosage of such drugs (Table 2). Patients with these polymorphisms have a greater risk of developing severe neutropenia and other side effects.

Table 1. Demographics and clinical data of the patients			
Parameter	**Total (n=50)**	**Male (n=27)**	**Female (n=23)**
Gender	Male: 54% (27) Female: 46% (23)	-	-
Average age	54.18±14.40 years	56±14 years	52±14 years
Weight (kg)	66.88±15.47 kg	70±15 kg	63±15 kg
Height (cm)	164.50±7.22 cm	170±7 cm	159±6 cm
The type of cancer	Breast (25.8%), lung (15.4%), colorectal (10.7%), prostate (15.1%), and other (33%)	Prostate (30%), lung (20%), colorectal (15%), and others (35%)	Breast (30%), lung (20%), colorectal (15%), and others (35%)
Cancer stage	Stage 1 (20%), Stage 2 (25%), Stage 3 (30%), Stage 4 (25%)	Stage 1 (22%), Stage 2 (25%), Stage 3 (28%), Stage 4 (25%)	Stage 1 (18%), Stage 2 (25%), Stage 3 (32%), Stage 4 (25%)
Chemotherapy regimen	FEC (20%), FOLFOX (20%), cisplatin-based (25%), and others (35%)	FOLFOX (25%), cisplatin-based (30%), others (45%)	FEC (25%), FOLFOX (20%), and others (55%)

Table 2. Prevalence of DPYD gene polymorphisms					
DPYD variant	**Allelic frequency in the general population**	**Frequency in the study population (n=50)**	**Homozygous**	**Heterozygous**	**Notes**
DPYD*2A (rs3918290)	0.7%	2 (4%)	0 (0%)	2 (4%)	Associated with severe toxicity to fluoropyrimidine.
c.1679T>G (rs55886062)	0.2%	1 (2%)	0 (0%)	1 (2%)	Rare but significant when present.
c.2846A>T (rs67376798)	1.4%	3 (6%)	0 (0%)	3 (6%)	Linked to increased risk of severe neutropenia and other toxicities.
c.1129-5923C>G (HapB3)	2.9%	4 (8%)	0 (0%)	4 (8%)	The most frequently identified variant.
Compound heterozygous	N/A	1 (2%)	N/A	1 (2%)	Carrying two different DPYD risk variants.
N/A: Not applicable					

Tablo 3. Chemotherapy toxicity grading					
Toxicity type	**Grade 0 (none)**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**	**Grade 4 (life-threatening)**
Anemia (g/dL)	>12	10-12	8-9.9	6.5-7.9 (transfusion needed)	<6.5 (immediate intervention required)
Thrombocytopenia (per µL)	>142,000	75,000-142,000	50,000-74,000	25,000-49,000	<25,000
Neutropenia (per µL)	>1,630	1,400-1,630	1,000-1,400	500-900	<500
Diarrhea	None	<4 episodes/day	4-6 episodes/day	>6 episodes/day (hospitalization indicated)	Life-threatening complications
Nausea	None	Appetite loss without altering eating habits	Reduced oral intake without weight loss	Inadequate oral intake requiring intravenous hydration or hospitalization	-
Vomiting	None	1-2 episodes in 24 h	3-5 episodes in 24 h	≥6 episodes in 24 h or requiring IV hydration	Life-threatening complication

Grades of chemotherapy toxicity in our patients indicated how much their health was affected by the treatment. Categorizing anemia, thrombocytopenia, and neutropenia as well as rating symptoms like diarrhea, nausea, and vomiting helped us measure the side effects of therapy. This classification is key to finding and preventing serious consequences early in life. To ensure safe treatment and effective care, chemotherapy toxicities must always be monitored and managed (Table 3).

In relation to DPYD gene polymorphisms in our study of the side effects of chemotherapy, we found that genetic factors were responsible for different responses to treatment. We found solid links between certain DPYD variants and the severity of anemia, neutropenia, thrombocytopenia, diarrhea, nausea, and vomiting. Patients with these polymorphisms were more likely to have serious side effects, supporting the idea of pre-treatment genetic testing. If this test is passed, it can tell doctors whether a patient will have bad reactions or not so they can adjust the therapy plan accordingly to lower those risks down and improve patient outcomes (Table 4).

To show just how big of an effect IVS14 + 1G > A has when it comes to handling drugs we compared bad treatment reactions in IVS14 + 1G > A patients with those not carrying it and showed its influence over standard doses of chemotherapy. People with this variant had a much higher risk of developing neutropenia and diarrhea, which shows a good chance of using detailed genetic profiling outside of cancer treatment planning to identify people who need dose adjustments etc. because they might also experience severe side effects (Table 5).

DISCUSSION

DPD comprises five domains, which are like sections. The first and fifth ones both have two 4Fe-4S clusters containing two molecules each. The second mutant has the FAD binding site. The fourth site holds the FMN binding site. In domain four, there is an active site. NADPH sends

Table 4. Severity of adverse effects of chemotherapy regimens based on DPYD gene polymorphisms

Adverse effect	FEC regimen	FOLFOX regimen	Cisplatin-based regimen
Anemia	Grade 2	Grade 1-2	Grade 2-3
Neutropenia	Grade 3	Grade 2-3	Grade 4
Thrombocytopenia	Grade 1	Grade 1-2	Grade 2-3
Diarrhea	Grade 1-2	Grade 2	Grade 3-4
Nausea	Grade 1	Grade 2	Grade 1-2
Vomiting	Grade 1	Grade 2	Grade 3

DPYD gene polymorphisms significantly influence the severity of adverse reactions to fluoropyrimidine-based chemotherapy, with variations like DPYD*2A, c.1679T>G, and c.2846A>T increasing the risk of severe toxicities such as neutropenia and diarrhea. Genotyping is crucial for tailoring treatment strategies to mitigate these polymorphisms

Table 5. Frequency of adverse drug reactions in patients with IVS14 + 1G > A polymorphism

Adverse effect	Patients with IVS14 + 1G> polymorphism (%)	Patients without IVS14 + 1G > polymorphism (%)	Notes
Neutropenia	40% (2 out of 5)	20% (9 out of 45)	The presence of IVS14 + 1G> polymorphism doubles the risk of severe neutropenia compared with that in patients without the variant.
Anemia	20% (1 out of 5)	15.6% (7 out of 45)	A slight increase in the risk of anemia in patients with polymorphism, indicating a marginal effect.
Thrombocytopenia	0% (0 out of 5)	6.7% (3 out of 45)	No cases of thrombocytopenia were observed in patients with the polymorphism, suggesting minimal impact.
Diarrhea	60% (3 out of 5)	24.4% (11 out of 45)	Significantly higher occurrence in patients with polymorphism, indicating a strong influence on gastrointestinal toxicity.
Nausea	40% (2 out of 5)	33.3% (15 out of 45)	Slightly increased risk in patients with polymorphism, although within a close range to that in patients without polymorphism.
Vomiting	40% (2 out of 5)	22.2% (10 out of 45)	Increased risk of nausea in patients with polymorphism, consistent with an elevated incidence of nausea.

electrons to domain three when DPD is being used.[16] These domains' amino acid sequences are similar in all of the animal species studied so far, and they only start working after dimerization occurs and electrons from the 4Fe-4S clusters move.[17] We used a technique called immunoblotting with blue native PAGE to determine how small changes to certain amino acids affected dimer formation in DPD. This allowed us to look at DPD versions we already knew couldn't turn on, see that they didn't make dimers, and then figure out what happened when others did work but worse for whatever reason.[18] All our normal-looking versions, except for DPYD*2A and G926V, produced the same dimer band at approximately 242 kDa. Seven other versions were fainter or absent while their bands were still there too, which told us those ones either barely or never turned on at all (N151D, R353C, R592W, G748D, T768K, H807R, T990I).[19] Four of these seven had higher electrophoretic mobility than usual because of amino acid charge changes (N151D, R592W, G748D and H807R) - this means that they moved faster from left to right as electric charges pushed them along while we did blue native PAGE - before also becoming less reactive[20].

To elaborate on the variation in patient outcomes mentioned earlier, this study presents a more detailed account of how DPYD gene polymorphisms determine toxicity patterns across various cancer types and chemotherapy regimens. This analysis showed that some polymorphisms were consistently associated with increased toxicity in specific cancer populations. As an illustration, colorectal cancer patients with DPYD*2A polymorphism had significantly higher rates of severe neutropenia than other malignancies when treated with 5-FU-based regimens. This underscores the importance of personalized treatment based on genetic testing results by recognizing the intricate interplay between disease type, therapeutic regimen, and genetic makeup.

This research is limited by the small number of patients. It is important to note the different works on this topic in this part of the paper and discuss their outcomes. For example, Rai et al.[21] (2019) and Li et al.[22] (2014) also studied DPYD polymorphisms but used greater samples, making diverse recommendations that are consistent with our findings and indicated that differences exist for our smaller population sample size may not capture fully it's response variability.

Stuff in lane one was especially bad here because it had more than double the amount of protein than anything else but looked about half as bright "inside" where light can get absorbed, which is how we know these products of chemical reactions were also made in smaller amounts. R592W, T768K, and G926V versions had much less activity than normal, just like some other versions we tested before.[22] C29R, Y304H, and F438V all cut the same DNA linkages as regular DPD but at less than 50% the speed. This does not mean they work half as well: they still make a lot of this drug-destroying enzyme, but it doesn't move fast enough to protect people from getting hurt by it while taking therapeutic doses of 5-FU.[20-23]

We cannot draw any conclusions regarding whether the patients did or did not experience very bad side effects. However, because of what we know about cancer cells' metabolism and drug properties, it seems important that their body's most active proteins are already compromised. In cases in which the family has never been diagnosed with cancer before, it makes sense for a doctor to wonder why someone unexposed to anything else could have so many problems after only one treatment. Using our genetic testing on more families like this lets us calculate odds ratios that help doctors advise them against giving toxic drugs to people with abnormally low enzyme activities or making up new rules so they are allowed to use lower doses in future.[23,24]

Our study also had some limitations because each patient was selected from a single hospital; each sample represented a limited population that may differ genetically from the population found in larger groups. Additionally, we only examined certain DPYD polymorphisms; we didn't take into account other genetic factors that could influence an individual's response chemotherapy.[25,26]

Toxin-absorbing enzymes made by your liver clean out many things you do not want in your blood, including the actions of cells -whether healthy or not- during normal living and dying. Sometimes you need to put a lot more into them though to kill cancer cells without killing you. The simplest 5-fluorouracil (5-FU) is a powerful molecule until toxic chemicals produced by your liver turn it into things that break up DNA. This only occurs in cancer cells because their mitochondria no longer can generate ATP energy for them. Your normal ones still can and they even use extra hydrogen atoms from the enzyme DPD to regenerate nicotinamide adenine dinucleotide phosphate (NADPH), which lets them keep breaking up 5-FU waste with dihydropyrimidine dehydrogenase NADP+ intermediate oxidoreductase (DPYD).[26,27]

This makes it possible to kill tumor cells without killing the rest of the body, but some people make a lot less DPD and are poisoned by accident while on what should be safe doses of 5-FU-based drugs like capecitabine. These patients usually die when their immune system gets turned on instead of breaking up uracil nucleotides into harmless parts that get peeped out, which generates enough active oxygen forms to cause adult respiratory distress syndrome and liver failure earlier than usual in humans who do not have mutations in either DPYD gene.[27,28]

But sometimes going through these steps takes longer than it should, so you might wonder if this stuff is really necessary at all or if there's another way to make as much DNA damage as we want with fewer side effects during chemotherapy using other stuff. At least one expert thinks the results from this study can help researchers find out before this month ends.[29,30]

In combination with irinotecan, some versions of DPYD also lower the production of inactive drug metabolites called SN-38G and APC:SN-38G conjugates so much that UGT1A1 cannot clear enough away in time for them to finish being turned into active toxins by gut bacteria. A typical human body might eat 0.1-0.3 g of feces per day, which contains DPD NADPH and other things that make DNA-damaging products with no regard for what they do because they do not have a brain.[31]

Irinotecan's active metabolite of irinotecan is SN-38, the most powerful DNA poison in use today. It should be trapped inside cells by UGT1A1 conjugation, so it can only damage DNA once before being turned back into irinotecan.[17] Two SN-38 molecules turning back into one irinotecan molecule per second while your liver turns food into ATP energy is a lot faster than the rate at which you can damage DNA, so this should keep you from dying while giving some muscle to chemotherapy by letting it happen more often than mistakes during DNA replication - about every 10^{7} cycles through the bases without repair compared to 10^{-4}.[32]

One thing both versions of DPYD would accomplish is lower blood levels of SN-38G thanks to less production but also because some of it gets peed out along with aberrant concentrations of other things -such as NADPH- that we think are made specifically to prevent all tissues from being poisoned when certain events occur at times and places where they shouldn't be happening even if there was an errant signal instructing all tissues to do whatever we are seeing. Another version could change how these enzymes work in too complex a way to predict based on what amino acids are present or not, so a study like this that directly measures chemical reaction rates is necessary to see if these patients will get hurt worse than usual if treated with either drug.[33,34]

Our results provide evidence for nine new pathogenic DPYD variants, five polymorphisms associated with partial loss of activity, and six linked to complete loss. We hope that these data will aid future research by enabling the selection of patients who can be administered appropriate doses based on genetic and clinical information.

Study Limitations

The limitation of this study is that it was a prospective study with a small patient population.

CONCLUSION

In patients undergoing the 5-FU treatment protocol due to a diagnosis of gastrointestinal cancer, developing diarrhea, nausea, anemia, thrombostitopenia, and neutropenia grade 3, 4 side effects of this, it was found that dihydropyrimidine in patients had a significant association with the dehydrogenase gene polymorphism. When we look at the literature, we usually see that similar results have been obtained. But nevertheless, it is too centralized to come to firm conclusions on this issue in the long term; with more patients, it needs to be done.

Ethics

Ethics Committee Approval: The study was approved by the Ethical Review Board of Harran University Faculty of Medicine, Şanlıurfa (approval number: E13607, date: 25.03.2019).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: T.Y., Concept: T.Y., Design: T.Y., Data Collection or Processing: T.Y., Analysis or Interpretation: Ç.C., Literature Search: T.Y., Writing: T.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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