



Association between *UGT1A1**28 Gene Polymorphism and Severe Neutropenia due to Colorectal Cancer Treatment with Irinotecan: Evidence Based on Meta-Analysis

*Associação entre o polimorfismo do gene UGT1A1*28 e a neutropenia severa decorrente do tratamento do câncer colorretal com irinotecano: evidências baseadas em meta-análise*

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Abstract

Objective The present study aimed to evaluate the relationship between *UGT1A1**28 gene polymorphism and the prevalence of neutropenia in patients with colorectal cancer treated with irinotecan.

Method Thirteen studies were included. These papers were selected from the Virtual Health Library, Scientific Electronic Library Online, International Health Sciences Literature and PubMed, and their data were collected and evaluated using the BioEstat 5.3 software (BioEstat, Belém, PA, Brazil).

Results Three genotypes were analyzed, namely 6/6 (wild type), 6/7, and 7/7. In total, 2,146 patients were included in the present study; of these, 55.6% ($n = 1,193$) had 6/6 genotype, 37.3% ($n = 801$) were heterozygous (6/7), and 7.1% ($n = 152$) had the 7/7 genotype. A total of 1,672 (77.9%) patients displayed mild neutropenia, whereas 474 (22.1%) had severe neutropenia. When contrasting the 6/7 and 7/7 genotypes with the 6/6 genotype using statistical tests for meta-analysis, patients with the 7 allele, either

Keywords

- neutropenia
- colorectal cancer
- polymorphisms

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in homozygosis or heterozygosis, presented higher risk of developing severe neutropenia than patients with the 6/6 genotype (odds ratio = 1.559; 95% confidence interval = 1.163–2.090; $p = 0.003$).

Conclusion The analysis of the *UGT1A1**28 gene polymorphism can aid the choice of treatment for patients with colorectal cancer in personalized medicine, increasing the chances of therapeutic success.

Resumo

Objetivo Avaliar a relação do polimorfismo do gene *UGT1A1**28 com a prevalência de neutropenia em pacientes com câncer colorretal submetidos a tratamento com o irinotecano.

Método Foram incluídos 13 estudos sobre o tema proposto, selecionados nas bases de dados da Biblioteca Virtual de Saúde, *Scientific Electronic Library Online*, *International Health Sciences Literature* e PubMed. Os dados foram coletados dos artigos científicos selecionados e avaliados com o auxílio do software BioEstat 5.3 (BioEstat, Belém, PA, Brasil).

Resultados Os genótipos analisados foram 6/6 (tipo selvagem), 6/7 e 7/7. Foram incluídos 2.146 pacientes. Destes, 55,6% ($n = 1.193$) apresentaram genótipo 6/6, 37,3% ($n = 801$) eram heterozigotos (6/7) e 7,1% ($n = 152$) tinham o genótipo 7/7. Um total de 1.672 (77,9%) pacientes apresentou neutropenia leve e 474 (22,1%) neutropenia severa. Ao contrastar os genótipos 6/7 e 7/7 com o 6/6, percebeu-se, com a execução dos testes estatísticos de meta-análise, que os pacientes com o alelo 7, em homozigose ou heterozigose, tinham maior risco de desenvolver neutropenia severa que pacientes com o genótipo 6/6 (razão de chances = 1,559; intervalo de confiança de 95% = 1,163–2,090; $p = 0,003$).

Conclusão A análise do polimorfismo do gene *UGT1A1**28 pode auxiliar na escolha do tratamento do paciente com câncer colorretal, no contexto da medicina personalizada, ampliando, assim, as chances de sucesso terapêutico.

Palavras-chave

- neutropenia
- câncer colorretal
- polimorfismos

Introduction

Colorectal cancer is the third most common type of neoplasm in men and the second most common in women; with the exception of non-melanoma skin cancer, it is the fourth main cause of cancer-related death worldwide.¹ Many studies have been carried out all over the world in an attempt to improve colorectal cancer prevention, diagnosis, and treatment, with increasingly satisfactory outcomes.²

The heterogeneity of this condition challenges the choice of the best treatment for a patient because numerous factors interfere with therapeutic success.² One of the most used chemotherapy agents is irinotecan, a topoisomerase I inhibitor with better therapeutic responses when compared with other drugs.³

The *UGT1A1* gene encodes an enzyme called uridine-5'-diphospho-glucuronosyltransferase (UGT), which inactivates and detoxifies SN-38, an active metabolite of irinotecan. Variations in *UGT1A1* associated with reduced enzyme activity result in an increased level of active metabolites in the bloodstream, increasing the risk of neutropenia, that is, a reduced number of neutrophils, which is observed in some patients.⁴ These variations can affect the pharmacokinetics of therapeutic agents because they do not encode the enzymes playing a metabolic role, directly influencing the achievement of desired effects.⁵

An additional TA repeat in the TATA sequence of the *UGT1A1* promoter region, which becomes (TA)₇TAA instead of (TA)₆TAA, characterizes *UGT1A1**28 polymorphism.⁶ The Food and Drug Administration (FDA) states that patients who are homozygous for the *UGT1A1**28 allele must receive 70% of the standard dose, gradually increasing according to neutrophil numbers. Heterozygous patients require no specific action.⁴

Advances in genetic studies and the greater knowledge regarding interactions between the patient's metabolism and the mechanism of action of chemotherapeutic substances will allow the use of an optimal drug, avoiding countless attempts to reach a specific treatment response.⁷

This study aimed to evaluate the relationship of the *UGT1A1**28 gene polymorphism with the prevalence of neutropenia in patients with colorectal cancer treated with irinotecan.

Method

The present study was carried out from a systematic review of the literature, using original articles on the incidence of neutropenia in patients treated with irinotecan and with *UGT1A1**28 gene polymorphisms. Through a meta-analysis methodology, studies were selected, and their data were extracted for statistical analysis, reducing the subjectivity from other review methods characterized as quantitative analyzes.⁸

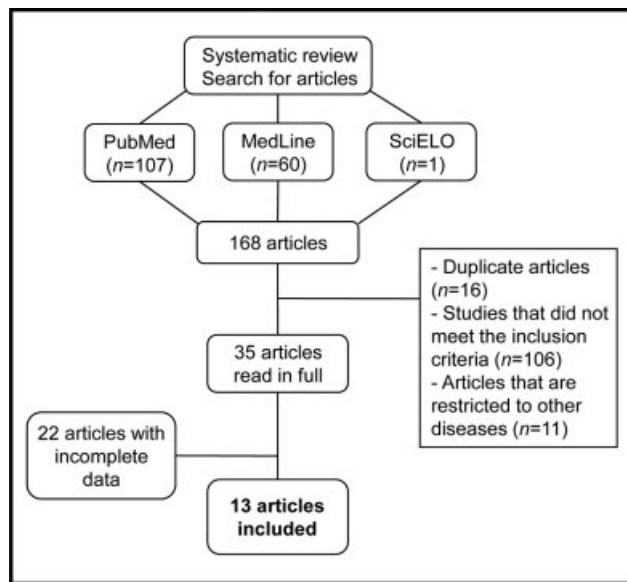


Fig. 1 Flowchart for paper selection.

Articles in Portuguese and English, published from 2007 to 2018, about *UGT1A1* polymorphisms and irinotecan-induced neutropenia in colorectal cancer were included to highlight the importance of genetic polymorphisms studies and their contribution to therapeutic improvement. Articles that did not mention polymorphisms associated with colorectal cancer or genetic factors that could result in cancer were excluded. Studies published in languages and time periods other than those defined in the inclusion criteria were also excluded (► **Figure 1**).

The following databases were queried: Virtual Health Library (VHL, also known as *Biblioteca Virtual em Saúde*, BVS), Scientific Electronic Library Online (SciELO), International Health

Sciences Literature (Medline) and PubMed from the National Center for Biotechnology Information (NCBI). In addition to papers published between 2007 and 2018, other articles were used for theoretical support and discussion.

After information collection, studies selection, and results extraction, an analysis of the data associated common aspects between *UGT1A1**28 gene polymorphism and irinotecan-induced neutropenia. Using the BioEstat 5.3 software (BioEstat, Belém, PA, Brazil), statistical tests for meta-analysis were applied to calculate the odds ratio (OR), 95% confidence interval (95% CI), and weight of each study and the combined sample. Significance was set at a 5% level.

Results

Data were collected from 13 studies, including a total of 2,146 patients, distributed as follows: 1,193 patients presented the 6/6 genotype, 801 were heterozygous, and 152 had the 7/7 genotype. Toxicity was classified as mild or severe neutropenia. Among patients treated with irinotecan, 1,672 (77.9%) had mild neutropenia and 474 (22.1%) presented severe neutropenia (► **Table 1**).

Contrasting 6/7 and 7/7 genotypes with the 6/6 genotype resulted in an odds ratio of 1.559 with a 95% confidence interval ranging from 1.1663 to 2.090 (► **Table 2**; ► **Figure 2**).

Discussion

Individual treatment warranted by genetic evidence is a widely accepted strategy, usually safe and with high chances of success. When evaluating polymorphisms and toxicity rates, we found a significant relationship between the 7 allele and the prevalence of severe neutropenia in patients with colorectal cancer treated with irinotecan.

Table 1 Severe neutropenia frequency per *UGT1A1**28 genotype

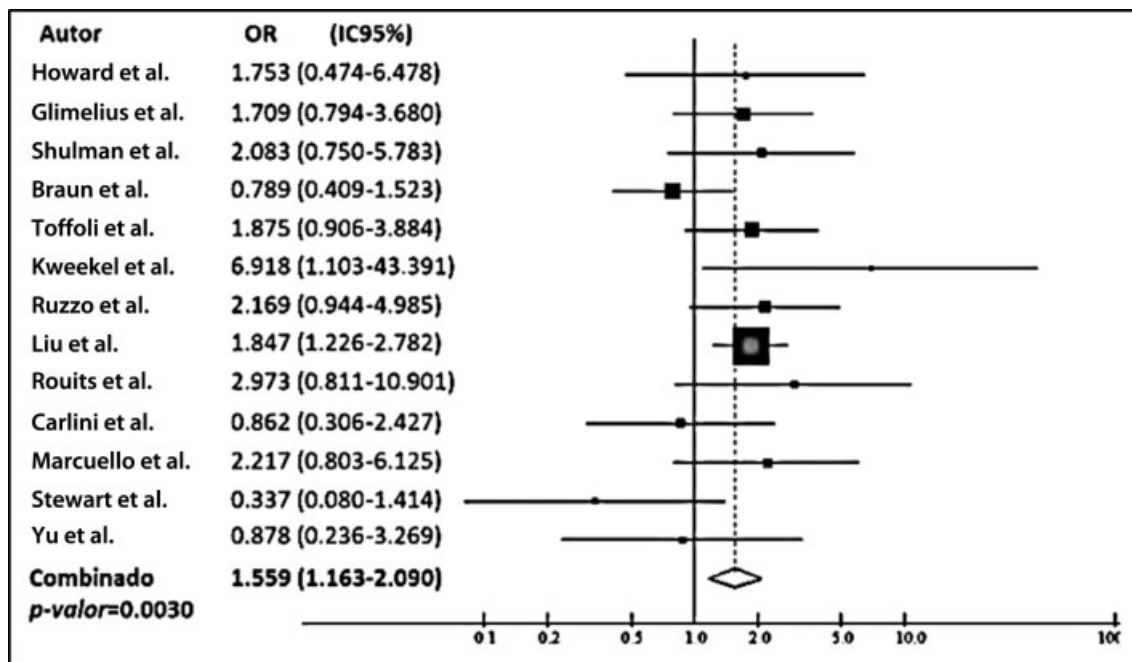
Authors	6/6			6/7			7/7		
	n	SN	f (%)	n	SN	f (%)	n	SN	f (%)
McLeod et al. ⁹	44	3	6.8	54	6	11.1	11	2	18.2
Glimelius et al. ¹⁰	72	15	20.8	51	13	25.5	13	7	53.8
Shulman et al. ⁶	91	5	5.5	98	8	8.2	25	6	24.0
Braun et al. ¹¹	79	57	72.2	68	44	64.7	20	15	75.0
Toffoli et al. ¹²	114	12	10.5	114	21	18.4	22	4	18.2
Kweekel et al. ¹³	46	1	2.2	31	6	19.4	3	0	0.0
Ruzzo et al. ¹⁴	59	9	15.3	72	13	18.1	15	12	80.0
Liu et al. ¹⁵	501	90	18.0	152	42	27.6	8	4	50.0
Rouits et al. ¹⁶	31	3	9.7	35	9	25.7	7	2	28.6
Carlini et al. ¹⁷	28	10	35.7	29	11	37.9	5	0	0.0
Marcuello et al. ¹⁸	40	6	15.0	45	12	26.7	10	4	40.0
Stewart et al. ¹⁹	27	5	18.5	36	3	8.3	9	0	0.0
Bai et al. ²⁰	61	11	18.0	16	2	12.5	4	1	25.0
Combined values	1,193	227	19.0	801	190	23.7	152	57	37.5

Abbreviations: f, Frequency; n, sample size; SN, severe neutropenia.

Table 2 Neutropenia-developing risk analysis per genotypes

Authors	6/6					6/7 + 7/7					OR	CI 95%		Weight
	n	MN	f (%)	SN	f (%)	n	MN	f (%)	SN	f (%)		Lower value	Upper value	
McLeod et al. ⁹	44	41	93.2	3	6.8	65	57	87.7	8	12.3	1.753	0.474	6.478	2.25
Glimelius et al. ¹⁰	72	57	79.2	15	20.8	64	44	68.8	20	31.3	1.709	0.794	3.680	6.53
Shulman et al. ⁶	91	86	94.5	5	5.5	123	109	88.6	14	11.4	2.083	0.750	5.783	3.68
Braun et al. ¹¹	79	22	27.8	57	72.2	88	29	33.0	59	67.0	0.789	0.409	1.523	8.89
Toffoli et al. ¹²	114	102	89.5	12	10.5	136	111	81.6	25	18.4	1.875	0.906	3.884	7.25
Kweekel et al. ¹³	46	45	97.8	1	2.2	34	28	82.4	6	17.6	6.918	1.103	43.391	1.14
Ruzzo et al. ¹⁴	59	50	84.7	9	15.3	87	62	71.3	25	28.7	2.169	0.944	4.985	5.55
Liu et al. ¹⁵	501	411	82.0	90	18.0	160	114	71.3	46	28.8	1.847	1.226	2.782	22.87
Rouits et al. ¹⁶	31	28	90.3	3	9.7	42	31	73.8	11	26.2	2.973	0.811	10.901	2.28
Carlini et al. ¹⁷	28	18	64.3	10	35.7	34	23	67.6	11	32.4	0.862	0.306	2.427	3.59
Marcuello et al. ¹⁸	40	34	85.0	6	15.0	55	39	70.9	16	29.1	2.217	0.803	6.125	3.72
Stewart et al. ¹⁹	27	22	81.5	5	18.5	45	42	93.3	3	6.7	0.337	0.080	1.414	1.87
Bai et al. ²⁰	61	50	82.0	11	18.0	20	17	85.0	3	15.0	0.878	0.236	3.269	2.22
Combined values	1193	966	81.0	227	19.0	953	706	74.1	247	25.9	1.559	1.163	2.090	p = 0.0030

Abbreviations: CI, Confidence interval; f, frequency; MN, mild neutropenia; n, sample size; OR, odds ratio; SN, severe neutropenia.


Fig. 2 Risk estimative for neutropenia development in patients with allele 7. Abbreviations: CI, confidence interval; OR, odds ratio.

At early therapy cycles, Toffoli et al.¹² found a relevant association in patients with 7/7 genotype to an increased risk for developing grade 3 or 4 neutropenia compared to patients with the 6/6 genotype. However, when evaluating the entire treatment cycle, no significant association with hematological and non-hematological toxicities was detected. Similar results were found by Braun,¹¹ who identified the influence of polymorphism only during the first 12 weeks of therapy.

Comparing patients with 6/6 and 6/7 genotypes, Rouits et al.¹⁶ found a higher frequency of severe neutropenia in patients homozygotic for the 7 allele. These authors also analyzed the risk of developing diarrhea, in which the genotype was not so influent as in neutropenia. When evaluating the relationship among polymorphism, neutropenia prevalence and chemotherapeutic agent dose in homozygous patients, reduced dosages resulted in no significant improvement.

Similar to the findings of our study, Côté et al.²¹ found a significant influence from the *UGT1A1**28 polymorphism but highlighted the -3156G>A polymorphism to better predict irinotecan toxicity during treatment. In addition, these authors recommend an up to 50% dose reduction in subjects with the 7 allele, especially homozygotes, resulting in lower toxicity and better therapeutic outcomes. However, information and studies on effective doses and which ones would lead to less toxic effects are scarce. There are few clinical studies on doses tailored by the patient's genotype and the presence of severe or mild neutropenia. An optimal scenario would be to evaluate the genetic polymorphism profile before chemotherapy institution to avoid exposure to severe toxicities that weaken the patient. Individualized treatments with accurate effectiveness are the goals of personalized medicine, using means, including genetic methods, to outline the best form of therapy while minimizing or abolishing toxicity.

Conclusion

The presence of the 7 allele increased the chance of severe neutropenia at approximately 1.5-fold in patients with colorectal cancer treated with irinotecan. Since an association with severe neutropenia was detected, chemotherapeutic agent pharmacokinetics and the genes involved in their metabolism must be studied in more details to find other types of polymorphisms in different genes.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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