IMPACT OF PHARMACOGENETICS ON THE TOXICITY OF HIGH-DOSE METHOTREXATE IN A PAEDIATRIC POPULATION

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BACKGROUND AND IMPORTANCE

The great inter-individual variability in relation to **toxicities** derived from **high-dose methotrexate (HDMTX)** treatment may be caused by **genetic variants** in genes involved in the metabolism and transport of methotrexate (MTX). The study of this variants involved in MTX pathway could help to **predict** the toxicity profile associated to HDMTX treatment.

AIM AND OBJECTIVES

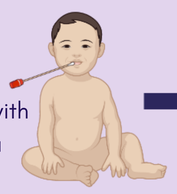
The **purpose** of this study was **to evaluate** the influence of **polymorphisms** in *MTR*, *MTRR*, *MTHFR*, *MTHFD1*, *ATIC* and *SLCO1B1* genes on the development of hepatic, hematologic and dermatologic **toxicities** among others, during the treatment with HDMTX in **pediatric oncology patients.**

MATERIALS AND METHODS

A **multicenter retrospective study** was carried out during 2021 in two **third-level hospitals**. The study has been approved by the **Ethics** and **Clinical Research Committee** of the Hospital with a prior i**nformed consent** of the patients for their inclusion in the study.

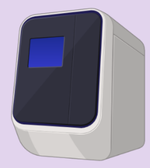
DNA collection

DNA extraction was performed from swabs with saliva samples using a QIAamp DNA Mini Kit.



Real time PCR

Polymorphisms were studied by via OpenArray™ by QuantStudio™ 12K Flex System using the "TaqMan™PGx Express" array



Patient data collection

Clinical-pathological characteristics and toxicities were obtained by reviewing the clinical history of the patients

Statistical analysis

Relation between pathological-clinical features, polymorphisms and toxicities to treatment with HDMTX were studied using bivariate analysis with Software R 4.1.1 version

RESULTS

A total of **64 patients** between **0-14 years old** treated with **HD-MTX** last 10 years **were included** in this study (Table 1).

- Patients carrying the **allele G** of *MTR* rs3768142 variant showed a higher probability of presenting **hepatotoxicity**, **gastrotoxicity** and **hemotoxicity**.
- The analysis showed that patients with the **allele G** of *MTRR* rs3768142 variant had a higher incidence of **hepatotoxicity**.
- In addition, the presence of the **allele A** in *MTHFR* rs1801133 gen polymorphism indicated the presence of **hemotoxicity**.

Table 1. Association between different toxicities and genetic polymorfisms in 64 patients diagnosed with cancer treated with HD-MTX.

Toxicity	Gen	SNPs	Genotype	N	NO N(%)	Yes (Grade 1-4) N(%)	X^2	p	Ref. Cat.	OR	CI 95%
Hepatotoxicity	*MTR*	rs3768142	G	39	13 (33.33)	26 (66.66)	7.352	0.007	G	4.25	1.45-12.42
	MTRR	rs1801394	G	46	25 (54,35)	21 (45.65)	3.667	0.05	AA	3.1	0.95-10.11
Gastrotoxicity	*MTR*	rs3768142	G	39	10 (25.64)	29 (74.36)	15.591	0.00001	G	9.18	2.96-29.46
Hemotoxicity	*MTHFR*	rs1801133	A	45	2 (4.44)	43 (95.56)	4.337	0.037	A	5.73	0.95-34.55
	MTR	rs3768142	G	39	1 (2.56)	38 (97.44)	5.451	0.0195	G	9.5	1.04-86.97

**p-value by Pearson's Chi-square test. OR: Probability of occurrence. CI: confidence interval.*

CONCLUSION AND RELEVANCE

The **results** obtained in this study suggest that patients who present some of the **polymorfisms** indicated above may present a **higher rate of toxicity** in paediatric oncology patients with HD-MTX treatment. **Further studies** are required in order to achieve an **individualized therapy** that provides greater efficacy and less toxicity to the treatment of these patients.

Ultimately, the main objective of this study was to demonstrate that the use of **pharmacokinetics** and **pharmacogenetics** information on methotrexate in paediatric patients diagnosed with malignant tumours allows the **optimisation** of treatment with this drug.

These results could generate a **significant benefit** and direct **clinical impact** for both the patient and the healthcare institutions by **reducing the incidence** and **severity of adverse effects** as well as **avoiding** treatment **failures**.

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