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

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 these 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 paediatric 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 informed consent of the patients for their inclusion in the study.

DNA collection

DNA extraction was performed from webbed with salivary samples using a QIAamp DNA Mini Kit.

Real time PCR

Polymorphisms were studied by TaqMan™ PGx Express” array via OpenArray™ by QuantStudio™ 12K Flex System using the “TeaMan™Dx Express” array.

Patient data collection

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

Statistical analysis

Relation between pathologic 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 rs5768142 variant showed a higher probability of presenting hepatotoxicity, gastrototoxicity and hematotoxicity.
- The analysis showed that patients with the allele G of MTRR rs1801133 variant had a higher incidence of hematotoxicity.
- In addition, the presence of the allele A in MTHFR rs1801133 gen polymorphism indicated the presence of hepatotoxicity.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Gen</th>
<th>SNPs</th>
<th>Genotype</th>
<th>NO (%)</th>
<th>NO NOS (%)</th>
<th>Yes (Grade 1-4) N (%)</th>
<th>X²</th>
<th>P</th>
<th>Ref.</th>
<th>OR</th>
<th>CI 95%</th>
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</thead>
<tbody>
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<td>Hepatotoxicity</td>
<td>MTR</td>
<td>rs3784182G</td>
<td>G</td>
<td>39</td>
<td>13 (33.3)</td>
<td>26 (66.6)</td>
<td>7.252</td>
<td>0.007</td>
<td>G</td>
<td>4.25</td>
<td>1.45-12.42</td>
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<td>MTRR</td>
<td>rs1801133A</td>
<td>G</td>
<td>46</td>
<td>25 (54.3)</td>
<td>26 (45.5)</td>
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<td>0.05</td>
<td>AA</td>
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<td>0.99-10.11</td>
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<tr>
<td>Gastrotoxicity</td>
<td>MTR</td>
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<td>G</td>
<td>39</td>
<td>10 (25.6)</td>
<td>29 (74.3)</td>
<td>15.991</td>
<td>0.0001</td>
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<td>2.96-29.46</td>
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<td></td>
<td>MTHFR</td>
<td>rs1801133A</td>
<td>A</td>
<td>45</td>
<td>2 (4.4)</td>
<td>43 (95.6)</td>
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<td>0.037</td>
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<td>0.95-34.55</td>
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<td>Hematotoxicity</td>
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<td>rs1801133A</td>
<td>A</td>
<td>45</td>
<td>12 (26.6)</td>
<td>38 (73.4)</td>
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<td>0.0195</td>
<td>G</td>
<td>9.5</td>
<td>1.04-86.97</td>
</tr>
</tbody>
</table>

*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 polymorphisms 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 optimization 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.

REFERENCES


