



# EXPLORING THE ROLE OF GENETIC VARIANTS IN ORAL MUCOSITIS IN PEDIATRIC PATIENTS RECEIVING CHEMOTHERAPY FOR LEUKEMIA AND LYMPHOMA

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## Objectives

This study aimed to investigate the association between genetic variants and the occurrence of OM in pediatric patients with acute lymphoblastic leukemia (ALL) and lymphoma undergoing methotrexate (MTX), cyclophosphamide (CTX) and doxorubicin (DOXO).

## Methods

64 ALL and lymphoma pediatric patients

392 cycles of CT (MTX/CTX/DOXO)

OM grade (WHO) +blood sample for DNA extraction

NGS - 67 coding regions spanning 20 candidate genes of CT metabolismo.

Comparison between the proportions and prevalence ratio of each genetic variant by their genotype model and the presence of oral mucositis according to protocol used.

| Gene           | SNV marker | Qui-quadrado p | Genotype | Multivariate Poisson regression PR [CI95%] | P  |
|----------------|------------|----------------|----------|--------------------------------------------|----|
| Presence of OM |            |                |          |                                            |    |
| MTX cycles     |            |                |          |                                            |    |
| ABCC1          | rs35587    | 34             |          |                                            |    |
| ABCC2          | rs2273697  | 4              | AG       | 0.09<br>(0.008-0.669)                      | 26 |
| ABCC2          | rs3740066  | 384            |          |                                            |    |
| ABCC2          | rs17222723 | 476            | CT       | 0.05<br>(0.003-0.57)                       | 18 |
| ABCC3          | rs1051640  | 5              |          |                                            |    |
| ABCC3          | rs2277624  | 4              |          |                                            |    |
| ABCC4          | rs2274405  | 2              |          |                                            |    |
| ABCC4          | rs2274406  | 1              | TT       | 18.81<br>(3.40-165.04)                     | 2  |
| ABCC6          | rs12931472 | 12             |          |                                            |    |
| CYP2A7         | rs4142867  | 336            |          |                                            |    |
| GSTM1          | rs1056806  | 21             | TT       | 0.11<br>(0.01-0.78)                        | 38 |
| GSTM1          | 147668562  | 29             |          |                                            |    |
| GSTP1          | rs4891     | 327            |          |                                            |    |
| MTHFR          | rs4846051  | 197            |          |                                            |    |
| SLC19A1        | rs1051266  | 475            |          |                                            |    |
| SLC19A1        | rs12659    | 174            |          |                                            |    |
| SLCO6A1        | rs10055840 | 480            |          |                                            |    |
| SLCO6A1        | rs6884141  | 277            |          |                                            |    |

## Results

Distribution of OM grades according to cycles of CT protocol.

| Protocol | DOXO predominating |      | MTX |      | CTX predominating |      | DOXO + MTX + CTX |      | CTX+DOXO |      | MTX+CTX |      | TOTAL |      |
|----------|--------------------|------|-----|------|-------------------|------|------------------|------|----------|------|---------|------|-------|------|
|          | N                  | %    | N   | %    | N                 | %    | N                | %    | N        | %    | N       | %    | N     | %    |
| OM       |                    |      |     |      |                   |      |                  |      |          |      |         |      |       |      |
| Grade 0  | 55                 | 41.0 | 37  | 33.9 | 26                | 38.2 | 8                | 17.8 | 3        | 15.0 | 5       | 31.2 | 134   | 34.2 |
| Grade 1  | 46                 | 34.3 | 36  | 33.1 | 22                | 32.4 | 6                | 13.3 | 7        | 35.0 | 5       | 31.2 | 122   | 31.1 |
| Grade 2  | 29                 | 21.5 | 31  | 28.4 | 16                | 23.5 | 17               | 37.8 | 6        | 30.0 | 1       | 6.3  | 100   | 25.5 |
| Grade 3  | 4                  | 3.0  | 5   | 4.6  | 4                 | 5.9  | 14               | 31.1 | 4        | 20.0 | 5       | 31.3 | 36    | 9.2  |
| TOTAL    | 134                |      | 109 |      | 68                |      | 45               |      | 20       |      | 16      |      | 392   |      |

|             |           |     |  |  |          |                      |  |  |  |  |  |     |  |
|-------------|-----------|-----|--|--|----------|----------------------|--|--|--|--|--|-----|--|
| CTX cycles  |           |     |  |  |          |                      |  |  |  |  |  |     |  |
| ABCC2       | rs2273697 | 217 |  |  |          |                      |  |  |  |  |  |     |  |
| ABCC6       | rs9940825 | 31  |  |  | TC       | 4.43<br>(1.36-16.13) |  |  |  |  |  | 166 |  |
| GSTP1       | rs1695    | 63  |  |  |          |                      |  |  |  |  |  |     |  |
| HSP90AA1    | rs4947    | 309 |  |  | AG       | 5.20<br>(1.43-22.75) |  |  |  |  |  | 178 |  |
| HSP90AA1    | rs8005905 | 425 |  |  |          |                      |  |  |  |  |  |     |  |
| SLC19A1     | rs1051266 | 102 |  |  |          |                      |  |  |  |  |  |     |  |
| SLC19A1     | rs12659   | 116 |  |  | AG       | 0.20<br>(0.05-0.64)  |  |  |  |  |  | 102 |  |
| DOXO cycles |           |     |  |  |          |                      |  |  |  |  |  |     |  |
| ABCC1       | rs35587   | 104 |  |  | CC or CT | 0.24<br>(0.07-0.638) |  |  |  |  |  | 68  |  |
| CYP2A7      | rs4079366 | 38  |  |  | CT or TT | 0.39<br>(0.17-0.84)  |  |  |  |  |  | 185 |  |
| CYP2A7      | rs4142867 | 130 |  |  |          |                      |  |  |  |  |  |     |  |
| MTHFR       | rs1801133 | 4   |  |  | AA       | 3.2<br>(1.20-9.59)   |  |  |  |  |  | 261 |  |

## Conclusion

Genetic variants may contribute to the development and severity of OM in pediatric patients undergoing chemotherapy. These findings emphasize the potential of pharmacogenetics in predicting chemotherapy-related toxicities and enabling personalized treatment strategies to improve outcomes.