Pharmacogenetics of childhood Acute Lymphoblastic Leukemia treated with Methotrexate

**BACKGROUND**

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy that affects blood cells and originates in the bone marrow, where haematopoeisis occurs. ALL is the most common form of childhood leukemia as well as the most common diagnosed childhood cancer (25-30%). This form of blood cancer is characterised by an overproduction of immature white blood cells, called lymphoblasts. Due to their immaturity, these malignant cells are unable to function properly to prevent and fight infection. Tumor cells are the result of a multi-step process of carcinogenesis and are characterized by being carriers of genetic alterations. This means that, together with their continuing proliferation, they accumulate in the bone marrow and arrest the production of healthy cells.

**Pharmacogenetics**

Aims to determine how the genetic makeup of each individual influences the response to drugs. Polymorphisms can modulate the response to a drug or therapy.

**Methodotrexate**

Methotrexate (MTX) belongs to the class of chemotherapy drugs called antimetabolites. In particular, they have the ability to join the cellular metabolism causing the cells to lose their ability to divide. Specifically, MTX is a folic acid antagonist.

**GENETIC VARIANTS**

- **MTHFR**
  - Cytogenetic Location: 1p36.3
  - Polymorphisms: 677C>T
  - Variant 677T
  - Genotype 677TT
  - Higher risk of relapse
  - ↓DFS 12-fold of developing toxicity

- **SLCO1B1**
  - Cytogenetic Location: 12p
  - Polymorphisms: rs4149081, rs11045879
  - Genotype rs4149081AA, rs11045879CC
  - High-MTX plasma concentrations
  - Clearance
  - Toxicity
  - ↓T521C V174A
  - Transporting activity
  - Weakening translocation of drugs from plasma to hepatocyte
  - ΔHepatic toxicity
  - ΔMTX plasma concentration

- **SLC19A1**
  - Cytogenetic Location: 21q22.3
  - Main transporter of MTX into cells
  - Polymorphisms: G80A
  - Variant 80A down, Variant 80G up
  - Uptake capacity for MTX
  - More efficient uptake MTX
  - Remission 3 times higher
  - ΔToxicity

- **ABCB1**
  - Cytogenetic Location: 7q21.12
  - P-Glycoprotein functional barrier
  - Polymorphisms: C3435T and G1199A
  - Variant 80AA down, Variant 80GG up
  - Uptake MTX
  - ΔP-EFS 83%
  - Protein expression
  - Risk of relapse 40%
  - pEFS 83%
  - ↑ALAT levels
  - Risk of relapse 61%
  - pEFS 78%
  - G1199GA
  - pEFS 83%
  - 2,9-fold higher risk of relapse

**CONCLUDING REMARKS**

- Despite some conflicting results, the mentioned polymorphisms in MTHFR, SLCO1B1, SLC19A1 and ABCB1 genes are considered to have an important potential for developing personalized medicine. However, further evaluation of the genetic polymorphisms is needed in order to definitely establish their effect on MTX treatment in ALL patients.
- MTX plasma concentration is thought to be associated with an increase of toxicity.
- Although positive associations between genetic polymorphisms and response to MTX treatment have been reported, we are still far from being able to apply pharmacogenetic tests in routine clinical practice.

**IDENTIFIED PROBLEMS**

1. Majority of studies has been developed with relatively small number of patients.
2. It has not been established a unified protocol for ALL treatment with MTX and research on the effect of each genetic variant.
3. Lack of consistency in quantifying the association between genotype and MTX response and toxicity.