Pharmacogenetics of childhood Acute Lymphoblastic Leukemia treated with Methotrexate

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The aim of the present poster is to review the actual state of knowledge of pharmacogenetics and childhood Acute Lymphoblastic Leukemia focused on treatment with Metrotrexate

BACKGROUND

Acute Lymphoblastic Leukemia (ALL) is a hematologic malignancy that affects blood cells and originates in the bone marrow, where haematopoiesis occurs. ALL is the most common form of childhood leukemia as well as the most common diagnosed childhood cancer (25-30%).

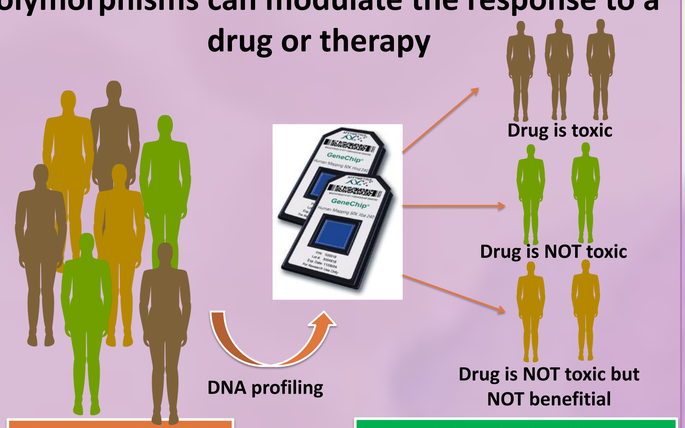
This form of blood cancer is characterised by an overproduction of immature white blood cells, called *lymphoblasts*. Due to their immaturity, these malignant cells are unable to function properly to prevent and fight infection.

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



Methotrexate

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.

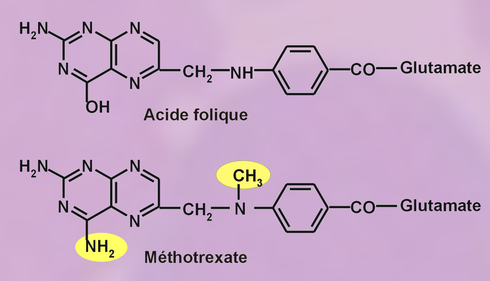


Figure 1. Folic acid and methotrexate only differ in an amino and a methyl-group

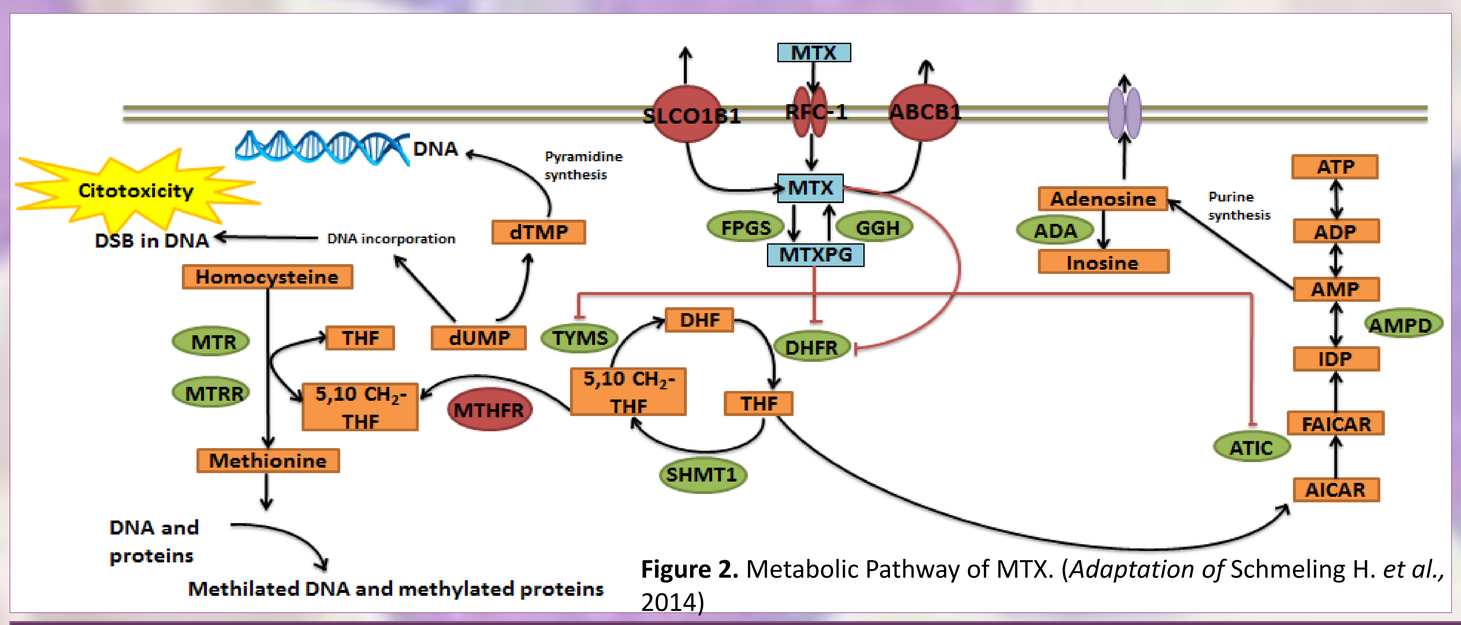
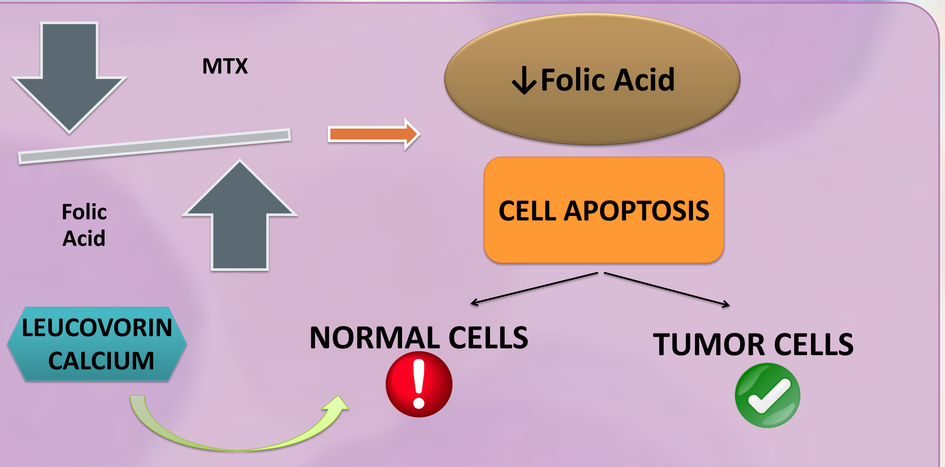


Figure 2. Metabolic Pathway of MTX. (*Adaptation of* Schmeling H. *et al.,* 2014)

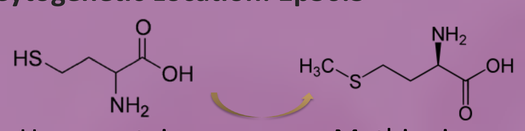


Leucovorin acts protecting healthy cells from MTX effects while allowing the entry of MTX into tumor cells to kill them.

GENETIC VARIANTS

MTHFR

- **Cytogenetic Location: 1p36.3**



- **Polymorphisms: 677C>T**

Variant 677T → Higher risk of relapse

Genotype 677TT → ↓DFS; 12-fold risk of developing toxicity

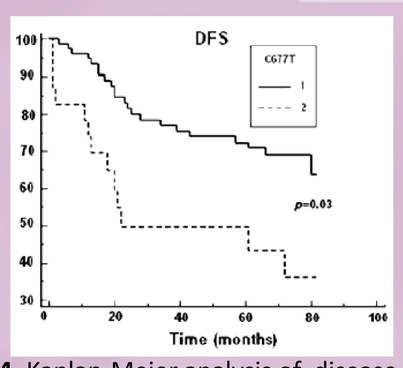
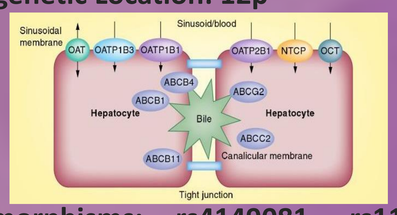


Figure 4. Kaplan-Meier analysis of disease-free survival and C677>T genotype [1 (CC+CT) versus 2 (TT)]. (D'Angelo V. *et al.,* 2011)

SLCO1B1

- **Cytogenetic Location: 12p**



- **Polymorphisms: rs4149081, rs11045879 and rs4149056**

Genotype rs4149081AA + **Genotype rs11045879CC** → High-MTX plasma concentrations → Clearance; Toxicity

rs4149056

T521C → V174A

↓ Transporting activity

Weakening translocation of drugs from plasma to hepatocyte

521TC+CC

- Δ Hepatic toxicity
- ↓Clearance
- Δ MTX plasma concentration

SLC19A1

- **Cytogenetic Location: 21q22.3**
- **Main transporter of MTX into cells**

- **Polymorphisms: G80A**

↓ Uptake capacity for MTX

Variant 80AA → More efficient uptake MTX; Remission 3 times higher; Δ Toxicity

Variant 80GG → ↓Uptake MTX

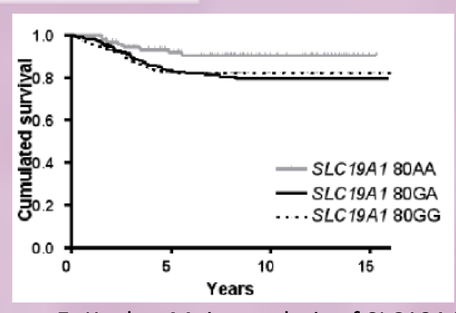


Figure 5. Kaplan-Meier analysis of SLC19A1 and outcome. (Gregers J. 2012)

ABCB1

- **Cytogenetic Location: 7q21.12**
- **P-Glycoprotein ⟶ functional barrier**

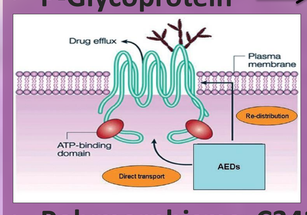


Figure 3. P-Glycoprotein structure. (Das A. *et al.* 2011)

- **Polymorphisms: C3435T and G1199A**

C3435T

3435TT/CT → ↓Protein expression; Risk of relapse 40%; pEFS 83%

3435CC → ↑ALAT levels; Risk of relapse 61%; pEFS 78%

G1199A

1199GG → pEFS 83%

1199GA → pEFS 68%; 2,9-fold higher risk of relapse

Affected outcome and protein function and expression

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 stablish their effect on MTX treatment in ALL patients.**
- **MTX plasma concentration is though 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 had 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.

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