PHARMACOGENETICS OF ACUTE LYMPHOBLASTIC LEUKAEMIA TREATMENT WITH THIOPURINES

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Introduction

Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer. This disease has 80-90% of cure rate. **Thiopurines** are one of the most used types of drugs in ALL therapy. The 6-MP is metabolized into 6-thioguanine nucleotides (6-TGNs) and into 6-methyl mercaptopurine nucleotides (6-MMPNs). Its antineoplastic property arises from the incorporation of 6-TGNs into DNA or RNA resulting in cell cycle arrest and apoptosis and the inhibition of *de novo* purine synthesis due to 6-MMPNs.

The balance between 6-TGNs and 6-MMPNs explains the major part of the toxicities of this treatment

The case of thiopurines for ALL therapy is a good example of **pharmacogenetics**. The aim of this science is to develop personalize treatments studying polymorphisms of genes involved in pharmacokinetics (drug metabolism) and pharmacodynamics (drug efficacy or toxicity).

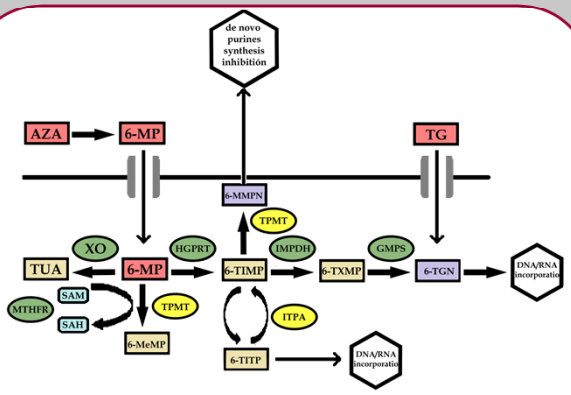

Figure 1: metabolism of thiopurines. Produgs are 6-mercaptopurine (6-MP), thioguanine (TG) and azathioprine (AZA).

Goals of the bibliographic research project

- How do polymorphisms in *TPMT* gene influence individual response to thiopurines?
- How is the situation of genotyping *TPMT* gene around the world? And in Spain?
- Are there other genes implicated in the pharmacogenetics of thiopurines?
- Which are the other consequencies of the polimorphisms of these genes?

Thiopurine S-methyltransferase (*TPMT*)

ALL patients treated with standard doses of thiopurines and with one or two non-functional allelic variants of *TPMT*

↓

Greater risk of dose-dependent myelotoxycity and a bigger likelihood of suffering secondary cancers[1]

↓

Genotyping tests and individualization adjustments in the dosage decease thiopurine adverse effects without compromising the efficacy

Thiopurine S-methyltransferase (TPMT) is a cytosolic enzyme that catalyses S-methylation of thiopurines. When TPMT activity is reduced or deficient , there is an accumulation of 6-TGNs because the S-methylation pathway is hardly inactivated.

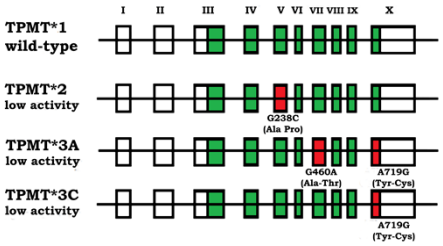

Figure 2: *TPMT* wild-type and three allelic variants implicated in the reduced activity of the TPMT protein

TPMT activity is also related with …

- At any given thiopurines dose intensity, intermediate and low TMPT activity → better **event-free survival (EFS)**[2]
- The incidence of **relapse** → not higher among *TMPT* heterozygous than wild-type homozygous[3]
- Homozygous wild-type *TPMT* → higher concentrations of 6-MMPNs → **hepatotoxicity**

At Spain, any hospital perform *TPMT* genotypage in ALL patients

St. Jude Children's Research Hospital

At some hospitals around the word, ALL patients are genotyped for *TPMT*

Clinical Pharmacogenetics Implementation Consortium (CPIC) dosage guidelines

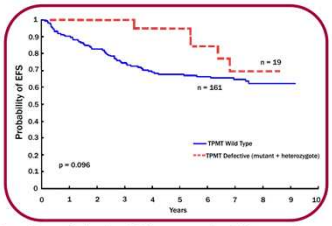

Figure 3: Kaplan-Meier curves for EFS according to *TPMT* status[2modified]

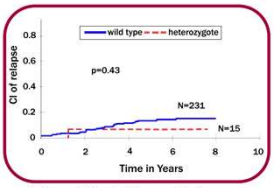

Figure 4: Cumulative incidence of relapse comparing *TPMT* heterozygotes and wild-type[3modified]

Other genes releated with pharmacogenetics of ALL

When ALL patients are homozygous wild-type for *TPMT* or when doses are adjusted for *TPMT* genotype, other genes have a significant influence on thiopurines-induced toxicity

Inosine triphosphate pyrophosphate (*ITPA*)

This is a cytosolic enzyme that catalyses the hydrolysis of 6-thioinosine triphosphate (6-TITP) to 6-thioinosine monophosphate (6-TIMP). When ITPA activity is reduced, there is an accumulation of 6-TITP (metabolized into 6-MMPNs by TPMT). Too much 6-MMPNs causes **febrile neutropenia**[4].

6-MMPNs concentrations	Lowest	Medium	Highest
TMPT and *ITPA* genotypes	Heterozygous *TPMT* WT homozygous *ITPA*	WT homozygous *TPMT* WT homozygous *ITPA*	WT homozygous *TPMT* Heterozygous *ITPA*

Allelic variant that reduced ITPA activity → ***ITPA* c.94C>A**

Other genes

Methylenetetrahydrofolate reductase (*MTHFR*)
The deficiency of this enzyme is related with **homocysteinuria**

Multi-drug resistance protein 4 (*MRP4*)
The deficiency of this nucleotide transporter increase the risk of a **6-TGNs accumulation**

Multilocus genotype *TPMT – SLCO1B1 – PACSIN2*
SNPs on these three genes found by a genome wide analysis are related with **gastrointestinal toxicity**[5]

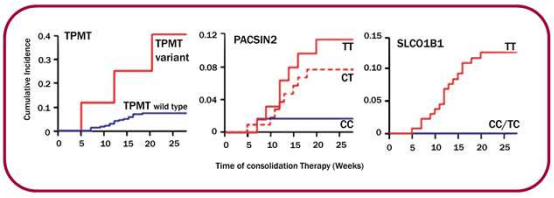

Figure 5: cumulative incidence of GI toxicity and the corresponding genotypes of *TPMT*, *PACSIN2* and *SLCO1B1*[5 modified]

Cost-effectiveness of genotyping *TPMT* gene

Analysis done by the Institute for Prospective Technological Studies (IPTS)

Germany Ireland Netherlands UK → Cost-effectiveness was defined as a cost per life-year gained → **2100€ per life-year gained**[6] ← Genotyping for *TPMT* gene in ALL patients prior to thiopurines treatment was highly cost-effectiveness

Conclusions and future purposes

- Some SNPs from *TPMT* gene cause a decrease of enzyme activity → toxic 6-TGNs accumulation
- At any hospital in Spain, *TPMT* genotypage is performed in ALL patients. In other hospitals like St. Jude Children's Research Hospital, ALL patients are genotyped for *TPMT*
- There are other genes related with the individual response to thiopurines → *ITPA, MTHFR, MRP4, SLCO1B1* and *PACSIN2*
- Polymorphisms on all these genes influence also other variables → event-free survival, relapse rates or secondary cancers
- More hospitals have to consider seriously genotyping *TPMT* as an essential part of therapy of ALL patients → genotyping costs are expected to decline in the future

We have the knowledge and the technology, so we should enforce it to the clinic to improve lives.

Bibliography

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