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 mercaptouracil 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 personalized treatments studying polymorphisms of genes involved in pharmacokinetics (drug metabolism) and pharmacodynamics (drug efficacy or toxicity).

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 consequences of the polymorphisms of these genes?

Thiopurine S-methyltransferase (TPMT)

- Thiopurine S-methyltransferase (TPMT) is a cytosolic enzyme that catalyses the metabolism of thiopurines. When TPMT activity is reduced or deficient, there is an accumulation of 6-TGNs because the 5-methyl pathway is hardly inactivated.

TPMT activity is also related with...

- At any thiopurines dose intensity, intermediate and low TPMT activity → better event-free survival (EFS)³.
- The incidence of relapse → not higher among TPMT heterozygous than wild-type homozgygous³.
- Homozygous wild-type TPMT → higher concentrations of 6-MMPNs → hepatotoxicity.

Cost-effectiveness of genotyping TPMT gene

Analysis done by the Institute for Prospective Technological Studies (IPTS) from Germany, Ireland, Netherlands and UK.

Cost-effectiveness was defined as a cost per life-year gained.

21,000€ per life-year gained.

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 genotypy 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, MRPA, SLC01B1 and PDCS2.
- 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