UNDERSTANDING LEUKEMIA

The role of CYP450 on Childhood Acute Lymphoblastic Leukemia

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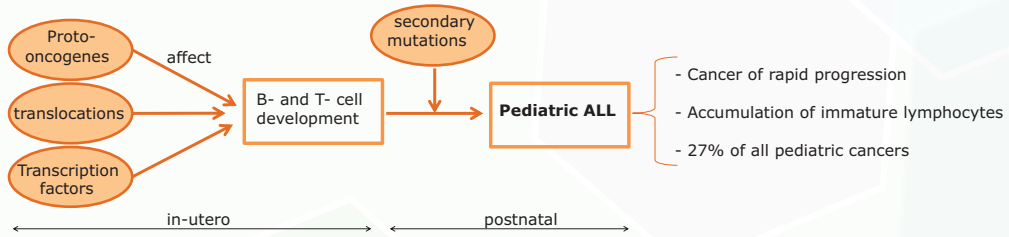
The aim of the present poster is to review the current knowledge about the known CYP 450 polymorphisms that alter response to drugs and treatment outcome of those pediatric patients with Acute Lymphoblastic Leukemia.

Childhood ALL

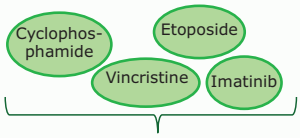
• ALL is the **most common pediatric malignancy**, and results from a multiple-step model of carcinogenesis.



• Cure rates have improved from less than 10% in the 1960s to 90% nowadays

Chemotherapy

The therapy for ALL consists of drugs with **highly toxic** profile



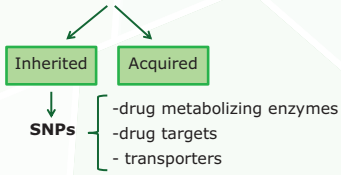
Direct toxicity produced in healthy tissue
↳ main cause of morbidity and mortality

Not all children treated respond equally to drugs
↳ **ethnic differences**

Pharmacogenetics

Seeks to define the **differences** between patients associated with treatment failure

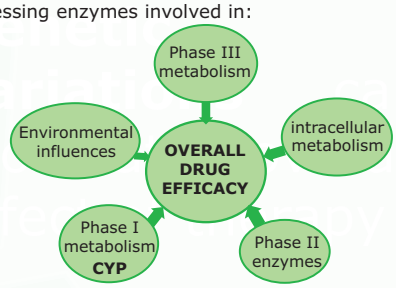
Genetic variations can modulate overall effect of therapy



Genetic polymorphisms modulate the **efficacy** of antileukemic agents and clinical **outcome** of ALL.

Drug Metabolism

drug efficacy is affected by a number of non-genetic and genetic influences, like SNPs in genes expressing enzymes involved in:



Cytochrome P450 (CYPs)

• enzymes responsible for most **phase I reactions**

• super family of **mono-oxygenases** → "activanting" molecular oxigen

• capable of catalyzing the **oxidative biotransformation** of xenobiotics
- drugs
- carcinogens

• 57 genes and 58 pseudogenes → 12 enzymes belonging to the 1, 2 and 3 CYP-families effectuate the metabolism of the majority of drugs

• **highly polymorphic**

CYP1 gene family

procarcinogen bioactivation induced by PAHs

CYP1A1

CYP1A1*2A

increased **risk** of ALL
worse therapeutic **outcome**
increased **incidence**
(+*GSTM1*, *GSTP1*)

CYP2 gene family

largest family of CYPs in humans
several of the most important drug metabolizing CYP

CYP2B6
CYP2B6*4
CYP2B6*2A
in association higher **toxicity**

CYP2D6
CYP2D6*4
Imatinib
reduced clearance
increased **adverse effects**

CYP2E1
CYP2E1*5
CYP2E1*3
contribute to its **incidence**

CYP3 gene family

the most well-studied CYPs in ALL
CYP3A induction increases drug clearance

CYP3A4
CYP3A4*1B
Cyclophos-phamide
induced **toxicity**
lower risk of secondary leukemia

CYP3A4*1B
CYP3A4*3C
Vincristine
decreased risk of peripheral neuropathy

CYP3A5
CYP3A5*3
Etoposide
in association with *GSTP1 Ile/Ile*
lower clearance drug

Conclusions and Future Perspectives

- multidisciplinary research is needed to understand both the biology of the disease and the host in order to prevent drug toxicity and adverse effects
- CYP enzymes have an important role in metabolizing drugs administrated to pediatric patients with ALL
- there is still a lack of evidence in regard to the true genetic contribution of CYP variants to the drug metabolism genotype
- further evaluation of the genetic variants reported in this project is needed in order to unequivocally establish their association with pediatric ALL

References

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Wall, A. M. & Rubnitz, J. E. Pharmacogenomic effects on therapy for acute lymphoblastic leukemia in children. Pharmacogenomics J. 3, 128–35 (2003).
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