

TYMS Overexpression in the Treatment of Childhood Acute Lymphoblastic Leukaemia. Is it a Prognostic Factor for Central Nervous System Relapses in Low Risk Patients?

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BACKGROUND

Acute Lymphoblastic Leukaemia

Acute Lymphoblastic Leukaemia (ALL) is a disease of lymphoid progenitor cells. It can affect both adults and kids, being the most common kind of cancer in children. It has an 80% cure ratio. Treatment failure is mostly related to relapses.¹ Children with ALL can be classified in risk groups (High and Low). If the subject has not any of the characteristics mentioned in *Table 1*, they will be classified as low risk.²

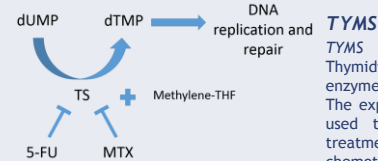
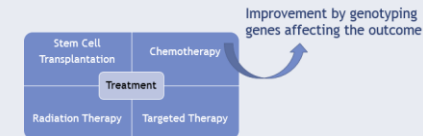


Figure 1: Methylation of dUMP to dTMP by TS, inhibited by drugs such as Fluorouracil (5-FU) and Methotrexate (MTX)

There are different *TYMS* alleles. The differences between them are located in the 5' Untranslated Region (UTR), where there is a tandem repeat of 28bp, including a Upstream Stimulating Factor (USF) family of E-boxes. Its number of repetitions affects the transcription and translation efficiency of the mRNA produced. There are two different alleles: double-repeat and triple-repeat (which increases the expression of TS). There is another polymorphism placed in the additional E-box of the triple-repeat allele. This one is a single nucleotide polymorphism (SNP) G→C, resulting in a double-repeat like TS expression.

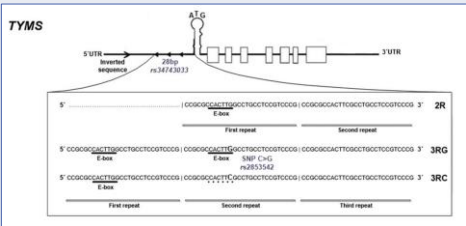


Figure 2: Structure of *TYMS* alleles. Adapted from previous report.⁴

Normal to medium TS expression

TYMS 2/2
TYMS 2/3(C or G)
TYMS 3C/3C
TYMS 3C/3G

High TS expression

TYMS 3G/3G

Table 2: Relationship between *TYMS* genotype and its phenotype.

High risk group characteristics

Age <1 or >10 years

Leukocyte count >50·10⁹/L

Central Nervous System (CNS) involvement

Testicular involvement

BCR-ABL t(9;22)

MLL-AF4 t(4;11)

E2A-PBX1 t(1;19)

Table 1: High risk group characteristics²

MATERIAL AND METHODS

Population

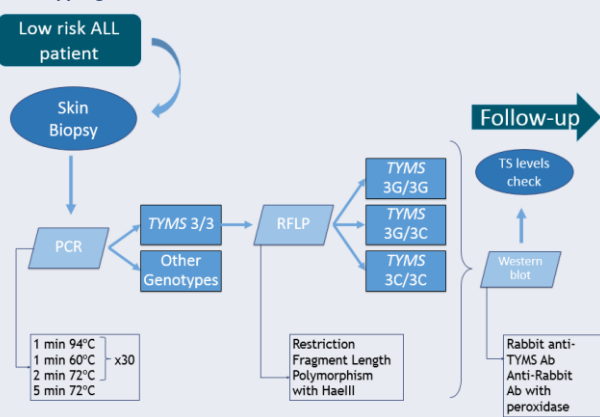
Subjects from one to ten years old, diagnosed with ALL and characterized as low risk, following the parameters from *Table 1*. A skin biopsy will be taken from every patient.

Follow-up

A follow-up will be made during their treatment, and for 5 years after ending it.

It will be described whether the subjects undergo any CNS metastasis or not.

Genotyping



Statistical analysis

Fisher's exact test performed in the R statistical computing environment will be done, testing the number of relapses versus the polymorphism that every subject has.

EXPECTED RESULTS

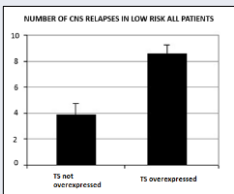


Figure 3: Expected number of CNS relapses regarding TS expression

It is expected to find a statistical significant relationship between the presence of *TYMS* overexpression and a higher probability of CNS relapses in patients with ALL treated with the low risk protocol.

HYPOTHESIS & OBJECTIVES

Hypothesis: *TYMS* overexpression decreases the effectiveness of the methotrexate treatment in childhood ALL, leading to a higher probability of CNS relapses on low risk patients.

Objectives:

- Characterizing a group of low risk patients with childhood ALL for the gene *TYMS*, and following up on their progression.
- Analysing the results of the follow-up, taking into consideration which polymorphisms every patient has.
- Proving if the genotype *TYMS* 3G/3G leads to a higher probability of CNS relapse in lower-risk group patients.
- Publishing the results to improve the treatment and follow-up of the children affected by ALL in hospitals.

DIFFUSION PLAN



- Publication of the report in *Blood Journal*.
- Show the results in the 57th American Society of Hematology Annual Meeting & Exposition in Orlando, Florida.

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