THE CLINICAL RELEVANCE OF INOSINE TRIPHOSPHATE PYROPHOSPHOHYDROLASE (ITPA) GENOTYPES IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction

Acute lymphoblastic leukemia (ALL) is a malignant lymphoid cells proliferation at early stage of differentiation, it is primarily a disease of children under six years of age; approximately 80-85% are of precursor B-cell phenotype.

With improvements in diagnosis and treatment, overall cure rate for children with ALL reached 85% in the developed world. Multiple recent studies indicate that genetic polymorphisms play an influential role in childhood ALL susceptibility, treatment response and prognosis.

The purine analog mercaptopurine is a key medication for the successful treatment of childhood ALL, Inosine triphosphate pyrophosphatase (ITPA) is one of several enzymes whose job is to cleanse the nucleotide pool. It catalyze the pyrophosphohydrolysis of 6-thioITP and methylthioITP and prevents the accumulation of such potentially toxic compounds. Therefore, the end result is that the ITPase enzyme acts to reduce the amount of active forms of the 6-MP drug present in human cells.

Characterization of ITPA deficiency by genotyping for the most common inactivating single-nucleotide polymorphisms can prospectively identify patients at higher risk of mercaptopurine toxicity which can subsequently influence the outcome of the patients.

Aim of the work

The aim of this study was to study the association of selected sequence variants in ITPA gene 94C>A (rs1127354) and IVS2+21A>C (rs7270101) with the clinical outcome in a cohort of pediatric ALL patients using 6-MP in their therapy.

Subjects

This study was conducted on 80 pediatric Acute Lymphoblastic Leukemia patients of both sexes admitted to Alexandria University Children Hospital.

Methods

Genotyping of ITPA gene for both 94C >A and IVS2+218 A >C polymorphisms using Real Time Quantitative Polymerase Chain Reaction (RQ-PCR).

Results

There was a highly statistical significant difference between relapse free survival and rs1127354 SNP genotypes (p=0.007) (table 1) ,while there was no statistical difference between overall survival and both ITPA SNPs.

Table 1: Relapse Free survival Kaplan-Meier in relation to ITPA genotypes

rs7270101	Mean	%	Log rank χ^2	Log rank p
AA	38.81	**79.3 %**	1.234	0.540
AC	41.87	**87.5 %**		
CC	–	**100 %**		
rs1127354				
AC	24.50	**50%**	7.260*	0.007*
CC	41.026	**85.8%**		

Table 2: overall survival Kaplan-Meier in relation to ITPA genotypes

rs7270101	Mean	%	Log rank χ^2	Log rank p
AA	35.75	**81.8%**	1.397	0.497
AC	39.99	**90.2%**		
CC	–	**100%**		
rs1127354				
AC	–	**100%**	0.347	0.556
CC	37.54	**84.1%**		

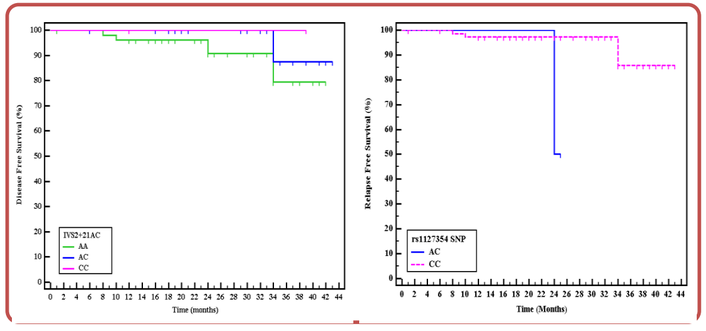

Figure 1: Relapse Free survival Kaplan-Meier in relation to ITPA genotypes

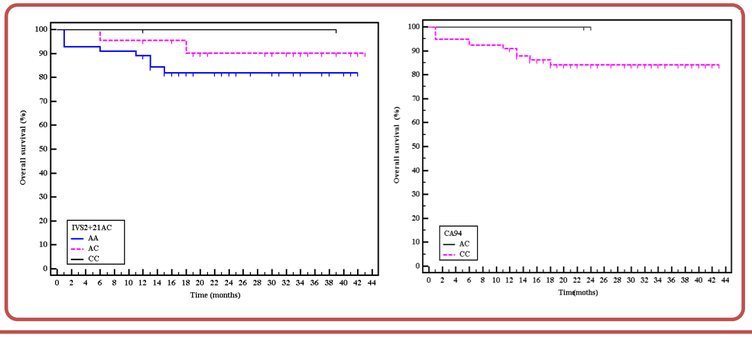

Figure 2: Overall survival Kaplan-Meier in relation to ITPA genotypes

Conclusion

ITPA polymorphisms 94C>A (rs1127354) was associated with lower relapse free survival.