CXCL10 gene promoter polymorphism A-1447G increase usceptibility to invasive aspergillosis in female oncohematological patients

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Invasive aspergillosis (IA) – is life-threatening invasive infection, especially in immunocompromised hosts, most of which are oncogematological patients. However it should be noted that the risk of infection and its clinical outcome vary significantly even among patients with similar predisposing clinical factors and microbiological exposure, implying an individualized genetic pattern of susceptibility.

The key components of fungal infections pathogenesis are disturbances of the immune system. Chemokine CXCL10, also known as interferon gamma-induced protein 10 (IP10), is a member of CXC chemokines. CXCL10 is an inflammatory mediator, which stimulates the directional migration of Th1 cells as well as increasing T-cell adhesion to endothelium.

CXCL10 gene is located at chromosome 4q21. *CXCL10* gene promoter single nucleotide polymorphisms (SNPs) affects protein expression via NF-kB transactivation.

The purpose of this study is to investigate the value of allelic variants A-1447G (rs 4508917) and G-135A (rs 56061981) *CXCL10* gene in risk of development IA in oncohematological patients in St. Petersburg.

Objectives

171 oncogematological patients on the background of cytostatic polychemotherapy with symptoms of lung injury were recruited to participate this study. 75 oncogematological patients (44,5%) either developed proven or probable IA as defined by criteria of EORTC/MSG 2008 (median age 43y ±14, range [22-77y], 57% males) whereas controls (96 oncogematological patients (55,5%) without IA comparable in age and sex) did not fulfill these criteria.

Table – Genotype frequency of polymorphism in oncogematological patients with IAL and without IAL

CXCL10 polymorphism	Control group (n=96)	IAL (n=75)	$\chi 2$, p value
A-1447G (rs 4508917)			
AA	39 (0,41)	29 (0,39)	$\chi 2 = 1.87$ p>0.05
AG	53 (0,56)	43 (0,57)	
GG	3 (0,03)	3 (0,04)	
G allele + ♀ sex			$\chi 2 = 3,853$, p<0.05, OR 3,13 95% CI (1,196 – 8,204)
G-135A (rs 4508917)			
GG	86 (0,91)	69 (0,96)	$\chi 2 = 1.73$ p>0.05
GA	9 (0,09)	3 (0,04)	
AA	-	-	

Methods

SNPs (rs 4508917 and rs 56061981) was analyzed by the method of restriction fragment length polymorphism (RFLP) analysis. Chemokine CXCL10 amount was determined by the enzyme-linked immunosorbent assay with the use of commercial ELISA kit sets (Cloud-Clone Corp, USA) and is presented in ng/ml serum. Statistical analysis was performed using SPSS 21 (IBM, USA).

Results

The genotype distribution of the studied SNPs is presented in the table. Although, there were no significant differences in genotype distribution of A-1447G and G-135A between oncogematological patients with probable IA and without IAL, when dividing patients by sex in a female group G allele was significant associated with the occurrence of IA ($\chi 2$=3.853, p<0.50, OR 3.13 95% CI (1.196-8.204).

There were no differences in serum CXCL10 levels between -135 GG and GA genotypes. However, individuals with -1447G allele had significantly higher serum levels of CXCL10 than those with -1447(A/A) genotype (p=0.022), Fig.1.

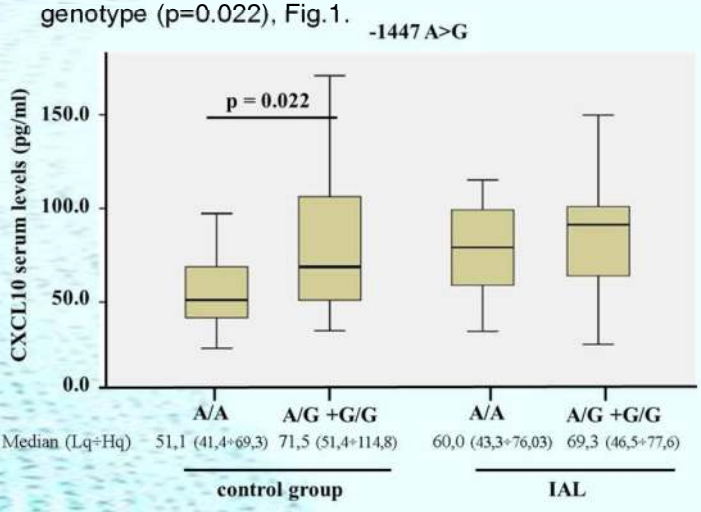

Fig.1 – Association between -1447A>G polymorphism with serum CXCL10 levels stratified by studied group

Conclusion

Further increase in the number of patients included in the study will allow to make conclusions about the prospect of typing the studied polymorphic variant of the gene CXCL10 as a predictive marker of the risk of mycosis development with a strong significance.

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