THE ROLE OF MANNOSE BINDING LECTIN AND THE RISK OF MORE FREQUENT EPISODES OF FEBRILE NEUTROPENIA IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction

Despite identical treatment protocols during childhood acute lymphoblastic leukemia (ALL) treatment, some children suffer from more frequent episodes of febrile neutropenia. The reason for this remains unknown. Constitutional expression of mannose binding lectin (MBL) has been correlated to infection susceptibility in a wide range of infections. However, the literature is showing conflicting results of the association between polymorphisms in the MBL gene (called MBL2 gene) and infections in children with cancer. Most studies investigating polymorphisms in the MBL2 gene in children with cancer have not used a homogenous cohort of patients. We therefore aimed to investigate this in children treated within the same treatment protocol during a 2.5 years long treatment for ALL. Our hypothesis is that polymorphisms in the MBL2 gene increases the risk for febrile neutropenia in this group of patients.

Figure 1: Included and excluded patients

Methods

Children diagnosed with ALL at Astrid Lindgren Children's hospital, Stockholm during the years 2004-2014 were retrospectively enrolled in the study. Children treated within the Nordic Society of Pediatric Hematology and Oncology (NOPHO) 2000 and 2008 treatment protocol were included. Three single nucleotide polymorphisms (SNPs) in the MBL2 gene were analyzed using pyrosequencing. The frequency of febrile neutropenia was retrospectively collected from medical records during the 2.5 years of treatment for ALL. Negative binomial regression was used to evaluate the association between the number of episodes of febrile neutropenia (dependent variable) and any polymorphism (explanatory variable).

Results

Ninety-seven children were enrolled in the study (Figure 1). Only the patients treated within the standard- and intermediate risk protocol were enrolled in the analysis. The median number of episodes of febrile neutropenia were 3 (range 0-10). Most commonly, the episodes of febrile neutropenia appeared during the beginning of the treatment where the chemotherapy is more intense (Figure 2). However, some patients also had repeated infections during the end of their treatment. The median age in the cohort was 4.8 years (range 1.1-17.9) and 52% were female.

Genotyping showed that 30 patients (31%) carried polymorphisms in one or more of the three investigated SNPs in the MBL2 gene.

Standard risk group

Intermediate risk group

Figure 2: Frequency of episodes of febrile neutropenia during the 2.5 years of treatment in children treated in the standard and intermediate risk groups of ALL. Red: NOPHO ALL 2000 protocol Blue: NOPHO ALL 2008 protocol

Preliminary statistical analyses do not show any statistical significant differences in frequency of febrile neutropenia when comparing those with polymorphisms in the MBL2 gene and those without, neither during the whole treatment period or the second maintenance phase, when analyzed separately.

Conclusions

In this homogenous cohort of patients treated for ALL, there were no correlation between polymorphisms in the MBL2 gene and risk for febrile neutropenia in the preliminary analyses.

Future

Extended gene analyses has been added, not only investigating the MBL2 gene but also polymorphisms in the gene coding for toll-like receptor 4 (TLR4) to see if there is any correlation between polymorphisms in the gene coding for TLR4 and risk for febrile neutropenia and the risk for neutropenic episodes. Also, polymorphisms in the genes coding for ITPA and NUDT15 have also been added to investigate if polymorphisms in these genes increase the risk for neutropenic episodes in this cohort of patients. Results are expected during summer 2018.

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