Severe Complications Due to THFR SNP in ALL T Type Recent Diagnosed Teenager, after Induction Protocol with Methotrexate: Case Report

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Submission: March 01, 2017; Published: June 01, 2017
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Abstract
Severe drugs toxicities in pediatric ALL patients could cause life-threatening situations and consequent PICU admission. Genomics and pharmacogenomics bring new insights on management and treatment. We describe a ALL pediatric patient with severe bone marrow aplasia with high blood levels of methotrexate after a standard IV dose for ALL induction block treatment.

Keywords: Leucemia children; Methotrexate adverse event; MTHFR

Introduction
There are 370 registered acute lymphoblastic leukemia (ALL) cases per year in Argentina, 30% of which will be admitted in PICU at some point of their disease history. Methotrexate is one of the drugs that ALL patients will be early exposed. Its metabolism by the MTHFR (methylene tetra hydrofolate reductase) is key to its clearance [1-4]. Over the past decades, the medical advance of genomics and pharmacogenetics enhanced the knowledge of drugs toxicity.

Case Report
A 13-year-old teenager with recently ALL diagnose is admitted to PICU with shock clinical signs after the first exposure to IV methotrexate (2gr) the patient initially required vasoactive drugs, antibiotic therapy and supplementary oxygen. Methotrexate toxicity was suspected therefore blood levels were measure, over 4 times expected levels were found. Folinic Acid rescue treatment started [5].

Figure 1: Describes the clinical evolution during PICU stay, White blood cell count (WBC) curve crossed with quantitative protein C is showed. The patient needed central line for IV multiple treatments, deep infection protocol was followed, candida albicans was found in the long term catheter (LTC) that was removed and replaced, Fusarium sp was found in skin infection. Total Parenteral Nutricion (TPN), vasoactive drugs were required.
Due to severe mucositis total parenteral nutrition was needed. White blood cell count descended since addition, after fifteen days at PICU the patient started with pancytopenia that persisted for 26 days; fever was associated therefore deep infection protocol was followed. Skin and mucosa infection by *Fusarium sp. And Candida albicans* in blood cultures were found. Total PICU days of stay were 61, days with TPN 35, antibiotics and antifungal were 45 Figure 1.

MTHFR’s Single nucleotide polymorphisms (SNPs) were analyzed, a mutation A1298C a (glutamic acid/ alanine change) was found. The patient continued with an alternative ALL treatment protocol, achieving remission. No PICU admission was needed again.

**Discussion**

Two MTHFR SNPs are associated with severe methotrexate toxicity, C677T and A1298C. Both, widely described in the literature as methotrexate metabolism inhibitor. Associated clinical manifestations are leucopenia and mucositis from moderated to severe. [1-8]. The patient described in this case report was found heterocygote for the A1298C SNP. Felice et al. described the association of mutations above with high risk of severe leucopenia in a pediatric population, encompassing different countries in a multicentre international study [9]. Latest recommendations on SNPs screening are not in GATLA protocols. SNPs for THFR are found mostly in jew population, Argentina has 1:238 6 highest ratio of Jews population per habitant in the world. The cost of the assay in Argentina, in a private clinical laboratory is around 40 US dollars (Man Lab, Argentina). Here and now, critical ill patients can benefit on their disease prognosis with the current knowledge on epigenetics, pharmacogenetics, custom biologics treatment, therefore these approaches are not the future any more, they should be thought about them also as prevention [10-12].

**References**