SPINAL CORD APLASIA CAUSED BY 6-MERCAPTOPURINE IN A CAUCASIAN GIRL WITH ACUTE LYMPHOBLASTIC LEUKAEMIA AND HOMOZYGOUS MUTATION IN NUDIX HYDROLASE 15: CASE REPORT

L.E. PINEDA LANCHEROS[1], C. PÉREZ RAMÍREZ[2], N. MORENO TORO[3], A. ESPINOSA RODRIGUEZ[4], A. SÁNCHEZ MARTÍN[4].

[1]PHARMACOGENETICS UNIT. PHARMACY SERVICE, UNIVERSITY HOSPITAL VIRGEN DE LAS NIEVES, GRANADA, SPAIN.
[2]PHARMACY SERVICE., UNIVERSITY HOSPITAL VIRGEN MACARENA, SEVILLA, SPAIN.
[3]PEDIATRIC ONCOHEMATOLOGY, UNIVERSITY HOSPITAL VIRGEN DE LAS NIEVES, GRANADA, SPAIN.
[4]PHARMACY SERVICE, UNIVERSITY HOSPITAL VIRGEN DE LAS NIEVES., GRANADA, SPAIN.

lepinedal@correo.ugr.es

4CPS-297

ATC code: L01 - Cytostatics

Background and importance

6-mercaptopurine (6-MP) is an anticancer and immunosuppressive agent used as part of the therapeutic strategy in acute lymphoblastic leukemia (ALL).

However, it may cause life-threatening **myelotoxicity**, that is commonly associated with **polymorphisms** in genes involved in its metabolism (thiopurine methyltransferase (*TPMT*) and nudix hydrolase 15 (*NUDT15*)).

Aim and objectives

To described a clinical case of a **Caucasian girl 2 years old diagnosed with B-ALL** (intermediate risk of hyperdiploidy in cytogenetics (DNI index 1.27) and MRD on day +15 of 1.4%. CNS-1)

She presented **prolonged myelotoxicity** under LAL-SEHOP-PETHEMA-2013 treatment protocol.

Material and methods

6-MP treatment

Induction phase

Occurred:
- Prolonged spinal cord aplasia
- Complication of sepsis due to *s. epidermidis*
- Required an Intensive Care Unit support

TPMT polymorphisms (*2, *3A, *3B and *3C) were studied without alterations.

Consolidation phase

Occurred:
- Aplasia
- Febrile neutropenia
- Respiratory infection
- Central venous catheter infection

The dose of 6-MP is reduced to 10%.

Reinduction phase

Occurred:
- Aplasia
- Febrile neutropenia
- Mucocutaneous infection by *Candida dubliniensis*

Maintenance phase

Occurred:
- Methotrexate and 6-MP were suspended several times
- 6-MP was resumed at 3% of the dose

She received multiple transfusions of red blood cells and platelets.

To understand the toxicity manifested by the patient and considering the update of the pharmacogenetic guide for thiopurines of the Clinical Pharmacogenetics Implementation Consortium (CPIC), **by taqman real-time PCR genotyping was performed for *NUDT15*-rs116855232 gene polymorphism.**

Results

Gene	Polymorphism	dbSNP ID	Variation type	Genotype	Phenotype
TPMT	*2: 238G>C	rs1800462	A80P	CC	Normal metabolizer
	*3B: 460 G>A	rs1800460	A154T	CC	
	*3C :719A>G	rs1142345	Y240C	TT	
NUDT15	415C>T	rs116855232	R139C	**TT**	**Poor metabolizer**

Recommended Dosing of Thiopurines by NUDT15 phenotype

Poor metabolizer: initiate dose at 10 mg/m2/day and adjust dose based on myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. If myelosuppression occurs, emphasis should be on reducing mercaptopurine over other agents.

This analysis revealed that the patient carriers the rs116855232-TT genotype (frequency in Europeans 0.000004). This polymorphism is associated with potentially fatal myelosuppression (evidence level 1A), which explains the toxicity manifested.

Conclusion and relevance

This case shows the relevance of **implementing pharmacogenetics studies** (*TPMT* and *NUDT15* gene polymorphisms) in the **daily clinical practice** that allows the early detection of patients treated with **6-MP** with higher **risk of suffering myelosuppression**

References: Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, Moyer AM, Evans WE, Klein TE, Antillon-Klussmann FG, Caudle KE, Kato M, Yeoh AEJ, Schmiegelow K, Yang JJ. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clin Pharmacol Ther. 2019 May;105(5):1095-1105.