Pharmacokinetics and therapeutic drug monitoring

P141 Individual dosing of carboplatin according to five formula used in a cohort of patients with ovarian cancer in real life

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Abstract - Introduction
Several formulae are used for individual carboplatin dosing, and no consensus to the choice of the most suitable formula is available. Five formulae are widely used: Calvert with estimation of Glomerular Filtration Rate with Cockcroft and Gault (Calvert) or CKD-EPI (Calvert CKD-EPI) or CKD-EPI with cystatin (Calvert-Cys), Chatelut, and the modified Thomas (Thomas) formulae (White-Koning et al. Cancer Chemotherapy and Pharmacology 2020). The aim of this study was to assess carboplatin dosing variation using five different formulae in real life.

Abstract - Material and method
A retrospective study of patients treated by carboplatin for ovarian cancer between February and December 2021 was realized. Demographic (age, weight, body mass index), medical and biological (stage disease, serum creatinine, cystatin C dosage) data were collected. Carboplatin dosing were calculated with the five formulae. The real carboplatin dose administered to the patient and the final formula used were recorded. The percentage of dose variation between the different formulas was calculated and compared with a non parameteric wilcoxon test for paired samples using Calvert-Cys as reference

Abstract - Results and discussion
46 patients were included, with a median age of 67 years [43-89]. Median BMI was 23.7kg/m² (15.4 to 40.6kg/m²), and median weight at baseline was 61.9kg (38.2 to 108kg). Patients were in advanced stage disease at 82.6% (stage 3 or 4 Figo). Carboplatin based treatment was in first line for 63% of patient and second line for 21.7%. A total of 339 carboplatin cycles was administered, with an average of 7 cycles per patient [2-18]. Calvert-Cys formula was the formula choiced for 81% of cycles. Differences statitically significant between Calvert-Cys carboplatin dosing vs. Chatelut formula were found ($p<0.001$; median variation (m.v): 9.1% [-29.7;77.1%]) but none with Calvert ($p=0.079$; m.v : -2.75% [-28.3 ;63.5%]), Calvert CKD-EPI ($p=0.45$; m.v: 1.7% [-18.2 ;52.9%]) and Thomas formulae ($p=0.092$; m.v :0.2% [-11.3 ;18.6%]). None carboplatine doses major variation (+/-20%) was found vs. Thomas formula but 36 versus Calvert, 22 versus Calvert CKD-EPI and 76 versus Chatelut formulae.

Abstract - Conclusion
Carboplatin doses calculated with Calvert-Cys formula were very close than those with Thomas but some case of major variation could be found with Calvert, Calvert CKD-EPI and Chatelut formulae possibly related to patients BMI (obese or cachectic). The clinical impact of the use of these formulae remains to be assessed.

P142 Day +7 asparaginase activity as a predictive value lla pediatric

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Abstract - Introduction
For a Pegylated E.coli asparaginase correct action in the pediatric LLA treatment , it is necessary that the activity trough level (day +14 post-administration) to be higher than 100 IU/l Salzer et al, 2108 has been postulated that the +7 day activity could be as a predictive value of that on day +14:
>500 IU/L do not monitoring on day +14.
100-500 IU/L monitoring on day +14
< 100 IU/L switch to Erwinia ASPase.
The aim of this study has been to show our experience with ASP-PEG activity and to validate of day +7 value activity like as predictive +14 value under routine clinical practice.

Abstract - Material and method
A prospective observational and multicenter study of 4 duration years, in which all patients, with LLA, under 18 years of age who received treatment with pegylated asparaginase (ASPase-PEG) were included.
The clinical and demographic data of the patients were obtained from their medical records. Blood sampling was performed on days +7 and +14 post ASPase-PEG administration. Asparaginase activity was determined using the validated MAAT® kit from Medac.

Abstract - Results and discussion
A total of 22 patients were included during the study period.
Fifty percent were male.
The mean age was 4.2 years (0-14).
72 plasmatic ASPase activity determinations was analyzed: 36 corresponding to the +7 value and 36 to the +14 value.
The mean value of activity on day +7 was 532.5 IU/L (998-262).
73.6% >500 IU/L
26.4% 100-500 IU/L.
All of +14 activity determinations was higer than 100 IU/L. The mean activity value on day +14 was 236.4 IU/L (355-122).
No silent inactivations were identified

Abstract - Conclusion
Our results indicate that, as had been described by Salzer et al , the +7 day plasmatic activity value may be used like a predictive value of +14 day activity and its determination could be used for early decision making in the face of silent inactivation situations.

P143 Pharmacokinetics of trastuzumab in patients with HER2+ gastric cancer

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Abstract - Introduction
As described in clinical trial TOGA, the treatment with Trastuzumab in combination with chemotherapy could be consider as standard option for patients wiER-2+ advanced gastric cancer. However, Cossion and Col (2014) suggested a worse response when Cmin1 plasmatic concentration of trastuzumab were under < 20 µg/ml which is consider the minimum level to block the most of HER2 receptors The aim of this study was to determinate trastuzumab plasmatic level (Cmin) in patients with HER2+ gastric cancer and the relationship of trastuzumab levels and patients' response in real clinical practice.

Abstract - Material and method
A multicenter, prospective, observational study of 4 years was carried out. Serum concentrations of trastuzumab were determined by immunoassay (SHIKARIÒQ-Tras®). Patients were classified in two groups according to trastuzumab Cmin: > 20 µg/ml or < 20 µg/ml. Data analysis was performed using SPSS ® version 22.2.

Abstract - Results and discussion
We wanted to show preliminary data results of a study which aim it is to analyze the relation between trastuzumab plasmatic levels and the treatment efficacy. Our data indicates that there is an inverse correlation between serum trastuzumab levels and patients weight. Also, it is possible that patient's sex could influence in achieving trastuzumab optimal levels.
Future analysis will be necessary to demonstrate if those levels could have influence in treatment efficacy.

65,7% (p=0,018). Similarly, only 14,2% of patients with a weight under 55 kg reached targeted serum level in contrast to 64,8% with higher weight (p=0,013).

Abstract - Conclusion
We wanted to show preliminary data results of a study which aim it is to analyze the relation between trastuzumab plasmatic levels and the treatment efficacy. Our data indicates that there is an inverse correlation between serum trastuzumab levels and patients weight. Also, it is possible that patient's sex could influence in achieving trastuzumab optimal levels.

144 DPYD gene mutation frequency in oncology patients in a tertiary hospital

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Abstract - Introduction
Dihydropyrimidine dehydrogenase encoded by the DPYD gene, is the rate-limiting enzyme of fluoropyrimidines catabolism.
Among around 450 missense DPYD single-nucleotide polymorphisms, only approximately twenty of them acquire a functional significance. Four of these variants are considered to be of clinical relevance for recognized effects on the protein, their identified higher risk of severe toxicity, and for their population frequency: rs3918290, rs55886062, rs67376798, rs56038477.
Aim: Detect the most frequent mutations that affect the DPYD gene in oncology patients in a tertiary hospital.

Abstract - Material and method
Observational, retrospective study carried out from July 2020 to December 2021. All patients who underwent a genotyping test for DYPD were included. Clinical and demographic variables were recorded: age, sex, and type of cancer. This study analyzes the loss-of-function variants in the DPYD gene: c.1905+1G>A (rs3918290) that identifies the DPYD*2A haplotype, and c.1679T>G (rs55886062) that identifies the DPYD*13 haplotype. It also studies the variants of reduced function: c.1129-5923C>G (rs56038477) that identifies the HapB3 haplotype and c.2846A>T (rs67376798).

Abstract - Results and discussion
We received 442 requests for DPYD gene determination with a mean age of 62.98±12.9 years, 50.68 % men. The most recurrent diagnoses were 33.94 % colon cancer, 29.41 % breast cancer, 20.36 % rectal cancer, 9.95 % pancreatic cancer, and 7.24 % gastric cancer.
One patient was heterozygous for the loss-of-function variants c.1905 + 1G> A, two patients were heterozygous for the reduced function variant c.2846A> T, and 16 patients were heterozygous for the decreased function variant c.1129-5923C> G, C.1236G>A and c.483+18G>A. Being, therefore, intermediate metabolizers who should receive a dose reduction of 50%.
The recommendation of dose individualization was accepted in 5 patients, in 6 patients the chemotherapy regimen was changed, in 7 patients adjuvant therapy was dismissed and two patients were not treated.

Abstract - Conclusion
In our center, we have routinely implemented the determination of these polymorphisms prior to the start of treatment with fluoropyrimidines, to identify these patients and avoid toxicities. DPD-deficient patients may experience serious side effects when treated with fluoropyrimidines and thus clinicians' decisions are influenced by the results of DYPD genotyping.

P145 TPMT and NUDT15 genotipe and azathioprine and mercaptopurine dose

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Abstract - Introduction
Thiopurines (azathioprine (AZA) and mercaptopurine (6-MP)) are used in inflammatory bowel disease (IBD) and acute lymphoblastic leukaemia (ALL) treatment.
In 2018 CPIC published a thiopurine adjustment dose, according to thiopurine methyl transferase (TPMT) and nudix hydrolase 15 (NUDT15) genotype.
The aim of the present study have been show the results of AZA and 6-MP individualisation program based on TPMT and NUDT15 genotype in both pathologies in the paediatric population.

Abstract - Material and method
This is a 5-year (2017-2022) prospective, multicentre and observational study , including patients under 18 years age diagnosed with IBD and ALL with AZA and 6-MP treatment.

DNAg extraction was performed by alkaline lysis (Ramos et al.(2015)) and genotyping was performed by real-time PCR using allele-specific fluorescence probes HybProbe® in LightCycler®480 termocicler

The polymorphisms analysed (SNPs) were:
TPMT(rs1800462; rs1800462; rs1800460; rs1142345; rs1800584)
NUDT15(rs116855232; rs147390019; rs554405994; rs186364861)

Abstract - Results and discussion
75 patients were included in the study, with a mean age 9.5 years and 54.6% male (35 ALL and 40 IBD).

16 patients were carriers (heterozygous) mutations, showing the following allele frequencies (%):

TPMT
*2= 0
*3B= 6,67
*3C= 10,67
*3A (3B+3C)= 6,67
*4= 0
NUDT15
*3= 1,33%
*4= 0
*6= 5,33%
*5= 0

In all mutated patients the recommended dose adjustment was performed The cost associated with the determinations was €12.5/patients, and the time required, including gDNA extraction was 4,5 hours.

Abstract - Conclusion
With this this program, it has been possible to identify patient carrying risk mutations of intoxication for to make dose adjustments were made before starting treatment.
The methodology developed allows its implementation in the daily routine of our hospitals, both for the simplicity of the technique and the associated costs.