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Introduction: Cytochrome P 450 enzymes (CYPs) were presumed to play a role in the oxidation of intermediate metabolites of busulfan (Bu). In vitro elucidation of involvement of CYPs in the oxidation of Bu metabolites is cumbersome due to the volatile nature of tetrahydrothiophene and nonavailability of sensitive quantitation methods. This study is aimed at exploring the association of CYP2C9, CYP2C19, CYP2B6, FMO genotypes, and sulfolane (Su) levels in children undergoing hematopoietic stem cell transplantation (HSCT). The relation of genotypes with the outcomes of HSCT was also explored.

Patients (or Materials) and Methods: Sixty-six children receiving IV Bu-based myeloablative conditioning regimen were genotyped for common functional variant alleles in CYP2C9 (*2 and *3), CYP2C19 (*2 and *17), FMO3 (rs2266780, rs2266782 and rs1736557), and CYP2B6 (*5 and *9). Plasma levels of Bu and its metabolite Su were measured after dose 9 from a subset of 44 patients for whom plasma samples after dose 9 were available. The ratio of Bu to Su was taken as a metabolic ratio (MR) to compare among genotype groups. The MRs (Bu/Su) and Su levels between different genotype groups were compared using nonparametric tests. The distribution of age, and gender between the groups was compared using t test and chi-square test, respectively. Cumulative incidence of overall survival and event-free survival were estimated using Kaplan-Meier curves and log-rank test was used to compare the difference between genotype groups or groups divided on the basis of MR, in a univariate analysis. Multivariate analysis was performed using cox-regression analysis.

Results: Higher metabolic ratios (MRs, Bu/Su) were observed in CYP2C9 *2 and *3 allele carriers (mean [SD], 7.8 [3.6] Vs 4.4 [2.2]; P = 0.003). Lower event-free survival was seen in patients with MR above the median (40% vs 79%; P = 0.009) and carrying reduced function alleles of CYP2B6 (40% vs 84%; P = 0.005).

Conclusion: This study suggests the role of the CYP2C9 in the oxidation reactions of THT and CYP genotypes along with Bu MRs to be important at predicting outcomes of Bu based myeloablative conditioning before HSCT.

Disclosure of Interest: None declared.

PP122—REGULATION OF HUMAN LEUKOCYTE ANTIGEN EXPRESSION AND NEVIRAPINE-INDUCED ADVERSE DRUG REACTIONS IN A MALAWIAN HIV-POSITIVE POPULATION

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Introduction: Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) widely used in antiretroviral therapy (ART) in sub-Saharan Africa. Approximately 5% of patients receiving NVP-containing regimens develop hypersensitivity reactions (HSRs). These can manifest as more severe reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and hepatotoxicity. Various human leukocyte antigen (HLA) alleles have been associated to NVP-induced HSRs in populations of differing ethnicity. Carriage of HLA-C*04:01 is associated with an increased risk of SJS in our Malawian cohort. We investigated whether expression levels of mir-148a, a microRNA known to regulate HLA-C expression, differ in serum samples from hypersensitive and tolerant patients. The aim of the study was to identify the role of posttranscriptional regulation of HLA-C expression in HLA-associated NVP-induced HSRs.

Patients (or Materials) and Methods: A total of 1117 HIV-positive patients in Malawi treated with a NVP-containing regimen were recruited prospectively. Of these, 57 patients developed NVP-induced HSRs. MicroRNA expression was analyzed using TaqMan probe-based qPCR in available serum samples of 41 tolerant and 33 hypersensitive patients. Expression levels were compared in hypersensitive patients at baseline (n = 19) and during the acute phase of the reaction (n = 26). Tolerant baseline (n = 25) and week 6 (n = 27) samples were used as controls. Data were analyzed using nonparametric tests.

Results: There was no significant difference in the baseline expression of mir-148a between tolerant and hypersensitive patients. In our cohort, mir-148a expression showed a 4.6-fold increase in acute hypersensitive samples, when compared with baseline hypersensitive (P = 0.008). This was not observed in samples from tolerant patients.

Conclusion: Our study has identified an increase in mir-148a expression levels in serum samples from Malawian nevirapine hypersensitive patients during the acute phase. The reason(s) for the change in expression during the acute phase are unclear but may be related to the ongoing inflammation associated with a HSR. Further investigation is required to elucidate the mechanism of the rise in microRNA levels and any implications this may have on the severity and duration of the HSR.

Disclosure of Interest: None declared.

PP123—TARGET GENE EVALUATION OF TWO MiRNAS DIFFERENTIALLY EXPRESSED IN FOCAL AND NON-FOCAL BRAIN TISSUE OF THERAPY-RESISTANT EPILEPSY PATIENTS

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Introduction: Resistance to anticonvulsants affects one third of all epilepsy patients. Limited bioavailability of the drug at the target site caused by increased expression of efflux transporters on the blood brain barrier or alterations of target genes as well as seizure-induced neural reorganization are potential mechanisms for therapy resistance. There is increasing evidence that expression of microRNAs (miRNAs) is deregulated in neuronal disorders. We hypothesize that an altered miRNA regulation of target genes is involved in drug resistance in epilepsy.

Patients (or Materials) and Methods: Hippocampal focal and cortical nonfocal brain tissue samples from 13 patients diagnosed with MTS (mesial temporal sclerosis) who underwent neurosurgery have been screened for miRNA expression using TaqMan® low-density arrays. To compare miRNA expression between brain regions, a Mann-Whitney U test was performed using R (Bioconductor). In silico approaches for both a hypothesis-based (efflux-transporter and target gene) as well as a hypothesis-free approach were used...