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ABSTRACTS COLLECTION

The 47th Annual Meeting of the European Society for Blood and Marrow Transplantation: Pharmacist Committee – Oral Session (O172-O174)

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Pharmacology Oral Session

O172.

Iron Chelation with Deferasirox Increases Busulfan Auc During Conditioning Chemotherapy Prior to Allogeneic Stem Cell Transplantation

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Background: Patients with hematological malignancies often suffer from iron overload due to repetitive blood transfusions and iron release during cytotoxic chemotherapy. Early treatment with iron chelators could potentially ameliorate the effects of acute iron toxicity (e.g., infection) and prevent long term impairment (e.g., organ fibrosis). In the setting of allogeneic hematopoietic stem cell transplantation (HSCT), chelation therapy is often postponed until the late posttransplant period because of potential drug interactions. Therefore, we conducted a study to investigate the influence of iron chelation with deferasirox on the pharmacokinetics of busulfan during conditioning therapy prior to HSCT.

Methods: Between November 2018 and August 2020, 25 patients with documented iron overload (serum ferritin >1000 µg/l) and planned HSCT after myeloablative, busulfan-based conditioning chemotherapy at the University Medical Center Hamburg-Eppendorf were enrolled in the study. They received 14 mg/kg/d deferasirox from the first day of conditioning until day 3 after HSCT. Busulfan was administered i.v. over 3 h with an initial dose of 3.2 mg/kg (based on AIBW in overweight patients) once daily. Four consecutive dosages were planned to achieve a cumulative area under the curve (AUC) of 80 mg/l*h. Therapeutic drug monitoring (TDM) was done on the first or second day of application and the busulfan dose was adjusted based on the results. TDM and subsequent dose adjustment were repeated if the necessary dose adjustment exceeded 25%.

Results: Patients were planned to receive busulfan with a median cumulative dose of 12.80 mg/kg (12.75–14.79 mg/kg). Prior to dose adjustment a calculated cumulative AUC of 93.7 mg/l*h (65.1–151.4 mg/l*h) was estimated with a median busulfan clearance of 0.134 l/h/kg (0.084–0.203 l/h/kg). The median deviation from the planned AUC was 13.7 mg/l*h (−14.9–71.4 mg/l*h). Busulfan dose adjustment was conducted once or repeatedly in 20 patients (80%). The median dose adjustment was −17.1% (−50.0–18.2%) and patients ultimately received busulfan with a median cumulative dose of 10.60 mg/kg (6.38–15.62 mg/kg). A busulfan dose reduction was necessary in 19 patients (76%) whereas a dose increase was only necessary in one patient. After dose adjustment the median AUC was 79.7 mg/l*h (62.5–84.2 mg/l*h) with a median deviation from the planned AUC of −0.3 mg/l*h

(−17.5–4.2 mg/l*h) and 23 patients (92%) reaching the targeted dose of AUC 80 mg/l*h ± 10%.

Conclusions: We demonstrate that it is feasible to administer deferasirox during busulfan-based conditioning regimen prior to HSCT if TDM of busulfan is performed. TDM is the key point to facilitate a safe co-administration of both medications since busulfan AUC is increased due to a low clearance by the simultaneous intake of deferasirox and dose reduction is indicated instead of the need for dose escalation of about 20% routinely observed in our patients otherwise. Because of the reduced clearance, a lower initial busulfan dose—for instance 2.65 mg/kg—with subsequent TDM could be considered in this setting.

Clinical Trial Registry: The trial was registered with the German Clinical Trials Register, number DRKS00015498, on October 10th, 2018.

Disclosure: FA received honoraria from Novartis. All other authors declare that they have no conflict of interest.

O173.

Does Treatment With Glucocorticoids Influence The Estimation of Glomerular Filtration Rate In Adults After Allogeneic Stem Cell Transplantation Using Cystatin C?

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Background: Estimation of the glomerular filtration rate (eGFR) is important for drug dosing, especially for those drugs with a narrow therapeutic index and mainly elimination by the kidneys. The majority of estimations are based on serum creatinine (crea), that is derived from muscles, and may therefore be false low in cachectic or malnourished patients, resulting in an overestimation of eGFR. An alternative endogenous marker is cystatin C (cysC), that is produced independently from nutrition and muscle mass and is suggested to be more reliable in cachectic patients. Though there are hints, that cysC-biosynthesis might be increased by glucocorticoids.

The aim of this study was to systematically analyse the differences of eGFR estimation using creatinine (crea-eGFR) or cystatine C (cysC-eGFR) in adult allo-HSCT patients with or without concurrent glucocorticoid medication.

Methods: According to a local policy cysC-eGFR was be determined once weekly in addition to crea-eGFR, both being calculated using the respective CKD-EPI formulas. All inpatients being stationary at 13.8.2020 and all patients with allo-HSCT from 1.11. to 30.11.2020 have been included in our analysis. Data were analysed anonymously using descriptive statistics.

Results: In 57 patients (35 male/22 female) with a median age of 55 years (range 19–79), a median weight of 76.4 kg (46.6–116.7) and a median BMI of 25 kg/m^2 (15–39) 231 samples could be analysed. In those 122 samples, when patients did not receive glucocorticoids, median crea-eGFR was 101 ml/min/1.73 m^2 (22–144), while cysC-eGFR was 60 ml/min/1.73 m^2 (17–128). At 109 sampling times, when patients received glucocorticoids, median crea-eGFR was 100 ml/min/1.73 m^2 (17–169) resulting in 13 samples (12%) with GFR stages 3 to 5 (<60 ml/min/1.73 m^2), while cysC-eGFR was 44 ml/min/1.73 m^2 (9–122) resulting in 80 samples (73%) with GFR stages 3 to 5 (<60 ml/min/1.73 m^2). Accordingly, differences between crea-eGFR and cysC-eGFR were significantly higher in patients receiving steroids (−37% vs. −51%, $p < 0.001$). This finding was mainly driven by samples from patients receiving methylprednisolone for treatment of GvHD ($n = 45$ [11 pat], median 90 vs. 39 ml/min/1.73 m^2, −60%), resulting in 35 (78%) samples with GFR stage 1 or 2 according to crea-GFR in contrast to 29 (64%) samples with GFR stage 3 and 13 (29%) samples with GFR stage 4 according to cysC-eGFR. The differences were smaller in samples of patients receiving methylprednisolone for SIRS prophylaxis during ATG ($n = 24$ [24 pat], median 104 vs. 52 ml/min/1.73 m^2, −47%) or antiemetic prophylaxis with dexamethasone ($n = 30$ [24 pat], median 108 vs. 59 ml/min/1.73 m^2, −43%).

Conclusions: The observed higher differences between crea-eGFR and cysC-eGFR in allo-HSCT patients receiving glucocorticoid treatment—especially for the treatment of GvHD—need to be considered in the determination of drug dosing, as there are huge variations in GFR stage and resulting dose adjustments. The observed generally lower cysC-eGFR is in our collective can be explained by the fact, that allo-HSCT patients are usually pretreated patients with malignancies and reduced muscle mass due to cachexia and/or malnutrition. The more pronounced difference in patients with GvHD receiving glucocortiods might reflect the even lower serum creatine levels as a result of steroid myopathy.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare

O174.

Oral Levetiracetam is Associated with Decreased Systemic Busulfan Exposure After Oral Dosing

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Background: Busulfan (BU) conditioning for hematopoietic stem cell transplantation (HSCT) may induce seizures, and prophylactic antiepileptic treatment is therefore recommended. Following updated guidelines, in August 2019 our adult HSCT department switched from phenytoin to oral levetiracetam prophylaxis during oral BU conditioning for levetiracetam's better safety profile and lower potential for drug-drug interactions. Since we have observed more patients with delayed absorption and lower Bu exposure (measured as area under the concentration over time curve [AUC]). We therefore systematically compared Bu pharmacokinetics after oral dosing before and after the switch in antiepileptic prophylaxis.

Methods: Retrospective cohort study in consecutive adults undergoing myoablative conditioning for HSCT with oral busulfan between August 2018 and August 2020 at our institution. We compared Bu PK after weight-based oral dosing (1 mg/kg adjusted body weight) in patients receiving phenytoin (during the year preceding the switch) with patients receiving levetiracetam (during the year following the switch). Bu AUC0-6 was determined by trapezoidal rule based on 10 samples taken during the 6-h dosing interval after the second BU dose. Bu PK parameters (AUC0-6, C0, Cmax, Tmax) were compared between the 2 groups by Wilcoxon rank-sum tests.

Results: We included 62 patients (35 men), 31 with phenytoin and levetiracetam prophylaxis each, median age 55 y (IQR, 42–62 y). There was no difference between treatment groups in age, sex distribution, weight, height, or dose/kg. Median AUC was significantly lower in the levetiracetam group (890 micM*min; IQR = 739–1076 micM*min) compared to the phenytoin group (1177 micM*min; IQR = 1076–1380 micM*min; $P < 0.001$; Figure). Similarly, C0 and Cmax were significantly lower in the levetiracetam group compared to the phenytoin group (both $P < 0.006$), but the difference in Tmax (median, 90 min for levetiracetam and 60 min for phenytoin) did not reach statistical significance ($P = 0.063$). In a multiple linear regression analysis, higher age ($P = 0.036$) and phenytoin treatment ($P < 0.001$) were associated with a higher AUC, while body weight, height, dose, and azole therapy were not.

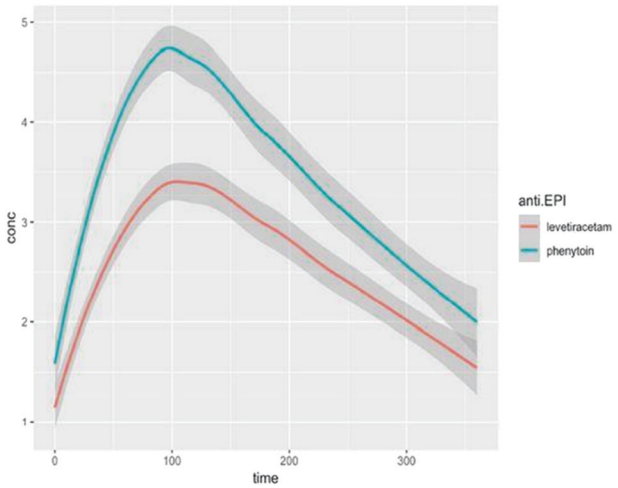

Figure: Busulfan concentration-over-time curves in the phenytoin group (blue line) and the levetiracetam group (red line). The lines were obtained by smoothing using the LOESS procedure, and 95% confidence intervals are represented in gray.

Conclusions: Our findings suggest that compared to phenytoin, oral levetiracetam reduces systemic exposure after oral Bu, most likely due to reduced bioavailability.

Disclosure: Nothing to declare