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ABSTRACTS COLLECTION

# The 46th Annual Meeting of the European Society for Blood and Marrow Transplantation: Pharmacist Committee Oral Session (O177-O178)



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## Pharmacology Oral Session

### O177.

### Evaluation of the Robustness of Therapeutic Drug Monitoring Coupled with Bayesian Forecasting of Busulfan with Regard to Inaccurate Documentation

*Adrin Dadkhah[1], Dzenefa Alihodzic[1], Astrid Broeker[2], Nicolaus Kroeger[1], Claudia Langebrake[1], Sebastian Wicha[2]*

[1]*University Hospital Hamburg-Eppendorf, Hamburg, Germany,* [2]*University of Hamburg, Hamburg, Germany*

**Background:** Inaccurate documentation of sampling and infusion times is a potential source of error in personalizing busulfan doses using therapeutic drug monitoring (TDM) coupled with Bayesian forecasting. Therefore, this study aims to evaluate the robustness of a limited sampling TDM of busulfan with regard to inaccurate documentation of sampling- and infusion times.

**Methods:** A pharmacometric study was conducted in NONMEM® and "R" by performing stochastic simulation and estimation (1000 simulations for 100 patients, 2 samples per patient) on the basis of a published population pharmacokinetic model. The dosing regimens consisted of 10 doses of i.v. busulfan (0.8 mg/kg) every 6h (Q6H) or 4 infusions with 3.2 mg/kg every 24h (Q24H) with a 2h- and 3h infusion rate, respectively. Planned sampling times after start of infusion were 2.5h + 5.5h for Q6H and 3.5h + 6.5h for Q24H. In order to evaluate the impact of inaccurate documentation, uncertainties were randomly added in "R" to the planned sampling times (standard deviation (SD) ± 5 min to ± 30 min) and infusion times (SD ± 20 min) before simulation. Estimation was carried out by using both accurate and planned times for sampling and for infusion time, as well as for the combination of both. Relative bias (rbias) and relative root mean-square error (rrmse) were calculated to determine accuracy and precision of the pharmacokinetic parameters clearance (CL) and volume of distribution (V) on the individual level.

**Results:** For Q24H, neither the estimates for CL nor for V were affected substantially by inaccurate documentation of sampling. Only when highly inaccurate sampling (SD ± 30 min) occurred simultaneously with inaccurate documentation of infusion time (SD ± 20 min), the rbias of V increased by 2.7% (0% accurate- vs 2.7% planned times). Similar results were found for the imprecision, where a deviation of 30 min between accurate and planned time alone resulted in an increased rrmse of 3.8% for CL and 4.1% for V. Regarding the combination of both uncertainties (± 30 min for sampling time and ± 20 min for infusion time) rrmse increased further for CL (+4.1%) and V (+4.3%).

In comparison, for Q6H calculated rbias of CL and V at an uncertainty of ± 30 min in sampling time differed 4.5% and 3.8% from accurate sampling. Also, if uncertain sampling time of ± 30 min was combined with ± 20 min

for infusion time, higher imprecisions for V were estimated (+5.4% rrmse).

**Conclusions:** Inaccurate documentation of sampling and infusion times only caused bias and imprecisions for both regimen if documented times for sampling and infusion times deviated from actual times as far as 30 min and 20 min, respectively. Furthermore, the calculated rbias and rrmse for CL and V indicate robustness for TDM of busulfan with only two samples, which not only lessens stress for patients due to fewer blood draws, but also decreases costs by requiring fewer bioanalytical assays.

However, the importance of accurate documentation should not be disregarded, as it is essential to Bayesian forecasting and therefore essential to personalizing busulfan doses.

**Disclosure:** Nothing to declare

## O178.

## Eltrombopag Therapy in Stem Cell Transplant Recipients Shows Effective Iron Mobilisation

***Igor Novitzky Basso[1,2,3], Evangelia Vlachodimitropoulou[3], Ivanovs Andrejs[1], Emmanouil Nikolousis[4], John Porter[5]***

*[1]Scottish Allogeneic Haematopoietic Stem Cell Transplant Unit, Glasgow, United Kingdom, [2]Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada, [3]University of Toronto, Toronto, Canada, [4]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom, [5]University College London, London, United Kingdom*

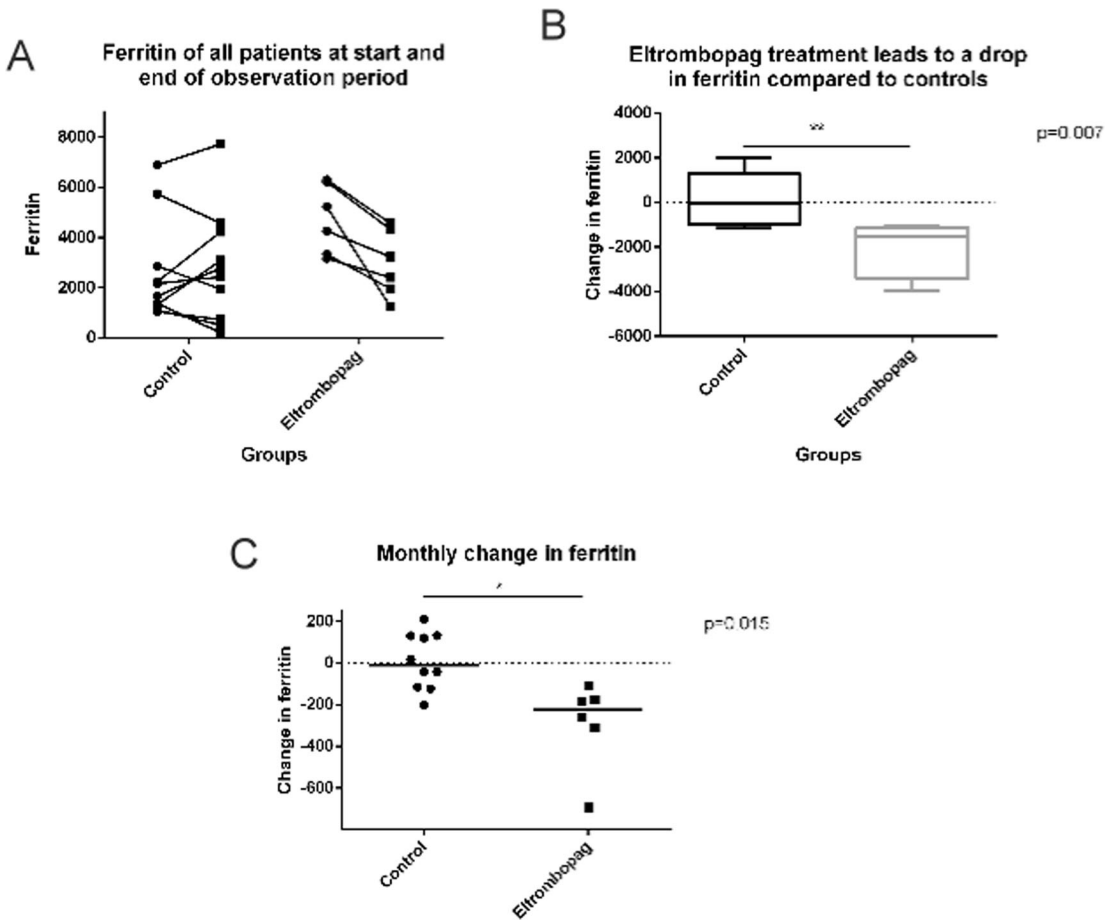
**Background:** Repeated blood transfusions, that are required by patients that have undergone stem cell transplantation (SCT), lead to the accumulation of body iron with a detrimental effect on survival (Meyer et al., 2013). This iron is removed by venesections or chelation and three iron chelators are licensed for clinical use namely: desferrioxamine, deferiprone and deferasirox. Eltrombopag (ELT), a small molecule agonist of the thrombopoietin receptor, is licensed for the treatment of chronic ITP, and has been shown to have clinically relevant effects in promoting stem cell function (Townsley et al., 2017). More recently, it has been shown to be a novel and effective iron chelator in a cell culture model (Vlachodimitropoulou et al., 2017).

Based on reports of good responses to ELT in post SCT patients with poor graft function (Dyba et al., 2016), a small cohort of SCT patients has received ELT at our centres, and we report the effect of ELT therapy on their iron stores.

**Methods:** Six patients (4 males, 2 females) with a median age of 53 years (25-61) received ELT post SCT for poor graft function (5, 50mg daily and 1, 100mg daily). Three patients had acute lymphoblastic leukemia (ALL), 1 myelodysplastic syndrome (MDS), 1 myeloproliferative neoplasm (MPN), and 1 non-Hodgkin lymphoma. Two patients had any grade of graft versus host disease. Ferritin was measured at the approximate start of ELT treatment, and at the time of ELT discontinuation. Five female and five male SCT controls with a median age of 48 years (33-54 years) and post-SCT ferritin >1000 from the same study period were randomly selected. Five patients had acute myeloid leukemia, 2 MPN, 2 ALL, and 1 MDS. Six patients had any grade of graft versus host disease. No patients were venesected. Median duration of ELT treatment was 6.4 months (2.5-10.2). Corresponding ferritin values for control patients were selected from 3 months post-SCT to a median of 9.5 months (4.46-14.6) post SCT. Analyses were undertaken using Mann-Whitney test for unequal variance.

**Results:** The ferritin trends of all individuals pre- and post-treatment with ELT are shown in Fig. 1a. The median change in ferritin following ELT treatment was −1551, compared to −28 in the control group ($p = 0.007$), Fig. 1b. The median monthly change in ferritin was −223.93, whereas it was −11.81 in the control group ($p = 0.015$), Fig. 1c.

**Conclusions:** The results of this small cohort analysis have shown a significant reduction in ferritin for ELT treated SCT patients in comparison to controls, reflecting a reduction in body iron stores, and supporting the in vitro data of ELT's novel role as a novel iron chelator. The rate of ferritin reduction supports its potential efficacy as an iron chelator, as highlighted in a report of plasma hypersiderraemia due to ELT (Caillon et al., 2019). Further studies, including tissue iron measurements by MRI, are required to establish the role of ELT in iron mobilisation, but this is promising data for heavily iron overloaded haemoglobinopathy patients, as well as those with bone marrow failure syndromes and iron overload.




[Figure 1]

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