2. NEWLY DIAGNOSED MULTIPLE MYELOMA

OPTIMIZATION OF MELPHALAN DOSAGE THROUGH ELIMINATION OF METABOLITES VIA HEMODIALYSIS IN MULTIPLE MYELOMA PATIENTS WITH RENAL IMPAIRMENT

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Background. High-dose Melphalan (MEL) therapy is mandatory in autologous stem cell transplantation for patients with multiple myeloma. In renal insufficiency MEL dosing is reduced to decrease toxicity, which will reduce the therapeutic effect. Renal removal of MEL itself is sparse and unpredictable. MEL is mainly converted into its metabolites monohydroxy-melphalan (MOH) and dihydroxy-melphalan (DOH) in the plasma. These metabolites are excreted by the kidneys and do not have cytotoxic activity but are thought to account for the drug's toxicity by substrate backlog. The aim of the study is to enable normal melphalan kinetics in patients with high-grade renal insufficiency through dialysis. Thus, we compared the pharmacokinetics of MEL and its metabolites in patients with and without parallel hemodialysis. Dosing of MEL was performed according to oncologic standard. Elimination kinetics were assessed by measuring the concentrations of MEL, MOH and DOH in the plasma, dialysate and urine.

Methods. To date, 20 patients have been evaluated, including 14 men and six women. The average age at MEL therapy was 58 years and the median GFR (CKDEPI) in the dialysis group was 31 ml/min (IQR 24.75 – 43.5 ml/min) and 80.5 ml/min (IQR 76.75 – 91.5 ml/min) in the control group. Overall, eight patients received MEL therapy with parallel hemodialysis. MEL was administered intravenously on two consecutive days. Patients in the dialysis group underwent hemodialysis following MEL administration for a total of four days. Concentrations of MEL, MOH and DOH were measured using mass spectrometry analysis (LC-MS/MS, 5500 Qtrap-system). A standardized cardio-oncological assessment was performed, including echocardiography, serial measurements of NT-proBNP and high-sensitivity troponin before and after MEL administration, 24-hour ECG monitoring, and baseline cardiovascular risk stratification using the HFA-ICOS (0=low, 1=moderate, 2=high, 3=very high) and H_2FPEF scores. Adverse events, the hematological and nephrological outcome were assessed every 3 months.

Results. The median administered MEL dose for the dialysis group was 174 mg and 199.5 mg for the control group. We observed a reduction of MEL and DOH of 84% and 56% over the course of dialysis, which was similar to patients in the control group with 89% and 51%. Due to its fast metabolization MOH was only detected in low concentrations which is consistent with findings from the literature. In urine the concentration of DOH was the highest among all three analytes after one day of melphalan administration which underlines the clinical relevance of renal excretion. No evidence of acute myocardial injury was observed, as high-sensitivity troponin remained stable (median 0.01 ng/mL), while NT-proBNP showed a clinically relevant increase (median 115 to 423 pg/mL), suggesting subclinical cardiac stress during high-dose melphalan therapy. Two episodes of atrial fibrillation occurred, both in the non-dialysis group. Thus, no evidence of accelerated myocardial injury or increased arrhythmic burden was observed. As well as cardiac side effects, the hematological and nephrological outcome did not differ significantly.

Conclusion. The elimination of melphalan and its metabolites via hemodialysis is effective, technically feasible and allows standard dosing of MEL even in patients with impaired renal function not already dependent on dialysis without an increase in toxic burden.