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LETTER TO THE EDITOR

Oxaliplatin pharmacokinetics on hemodialysis in a patient with diffuse large B cell lymphoma

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Dear Editor,

Oxaliplatin is a widely used chemotherapeutic agent in diverse anticancer regimens [1]. As oxaliplatin is eliminated from the body mainly by the kidneys and its clearance strongly correlates with glomerular filtration rate (GFR), patients with renal insufficiency or end stage renal disease (ESRD) are especially prone to accumulation and drug-related toxicity [2]. However, the role of extra-corporal renal replacement therapy in oxaliplatin clearance is not clear. So far, pharmacokinetic data is limited to single hemodialysis (HD) treatment cycles and their respective effect on plasma total and plasma free platinum levels [3, 4]. However, there is no data available on the absolute clearance of oxaliplatin from the body by HD, and HD dose as a parameter of oxaliplatin clearance has not been studied so far. Furthermore, long-term effects of HD on oxaliplatin elimination and necessary dose adjustments are lacking.

We analyzed oxaliplatin clearances in a 61-year-old anuric HD patient who was referred to our tertiary care hospital in April 2014 with cervical, supraclavicular, and retroperitoneal lymphadenopathy. Histology revealed follicular lymphoma grade 3A, stage IIIA. Due to additional cardiovascular comorbidity, the patient received six courses of rituximab and bendamustine, which led to partial remission as best response. Despite rituximab maintenance, clinical relapse with recurrence in the known localisations plus splenic infiltration and histopathological transformation to diffuse large B cell lymphoma occurred in September 2015. Second-line treatment with rituximab, gemcitabine, and oxaliplatin was chosen. Because of ESRD secondary to polycystic kidney disease requiring regular home HD since 2002 and lack of evidence for long-term oxaliplatin clearance, dosage of oxaliplatin was reduced to 50 mg/m^2 (50 % reduction, Fig. 1b).

Sample collection comprised spent dialysate, ultrafiltrate, and serum. Results (Fig. 1a) show a C_{max} of total predialyzer serum platinum (1093 μg/L) within the therapeutic range (500–5000 μg/L) before start of HD and a rapid exponential decline during 5 h of HD, which is in line with data from the literature [4]. Pre- and post-dialyzer platinum concentrations converged after 4–5 h of dialysis with ΔAUC (AUC_{pre}−AUC_{post}) representing platinum removal on HD. Concentrations after the first and before the second HD did not change significantly, indicating that no additional elimination occurred between day 1 and 2 after oxaliplatin application. Although calculated dialyzer clearance of oxaliplatin (CL_{dial}) was relatively low (28.43 mL/min), daily dialysis over five consecutive days clearly showed a significant reduction of long-term platinum serum concentration (Fig. 1b). Interestingly, total amounts of platinum in ultrafiltrate (153 μg) and spent dialysate (4815 μg) were unexpectedly low, which may be

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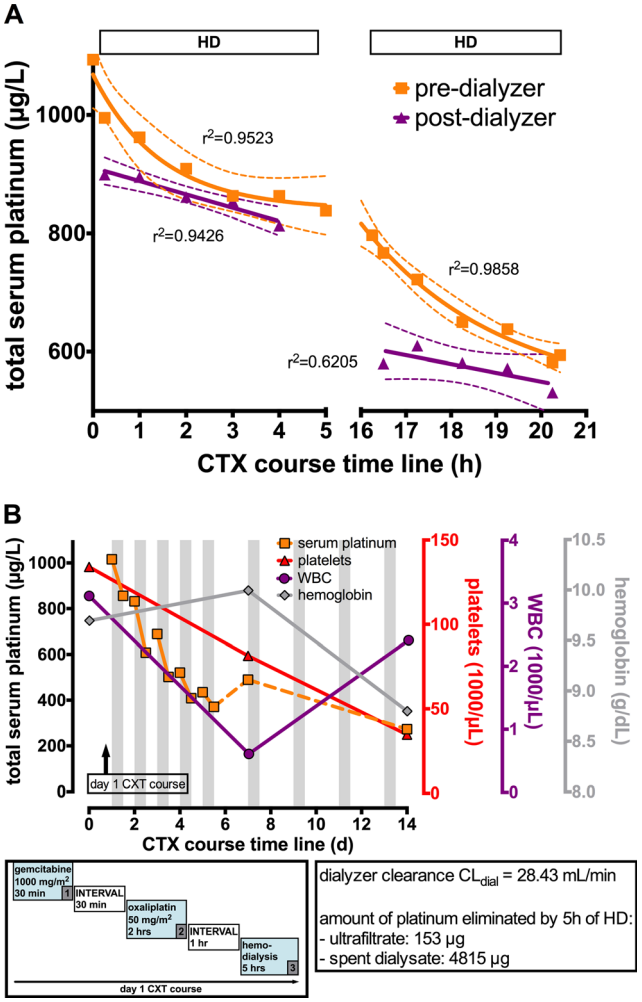

Fig. 1 **a** Clearance of pre-dialyzer serum platinum on days 1 and 2 after oxaliplatin administration (50 mg/m^2) follows an exponential decay relationship. Post-dialyzer serum platinum is best described linearly. **b** Platinum clearance by daily HD on five consecutive days reduces platinum levels to 50 % of C_{max}. Pharmacokinetic sample collection included spent dialysate, ultrafiltrate, serum before and after HD as well as pre- and post-dialyzer after 15, 60, 120, 180, and 240 min of HD, respectively. Total plasma concentrations were quantified by inductively coupled plasma mass spectrometry. HD was performed as high-flux bicarbonate dialysis (GENIUS dialysis system, F60S polysulfone high-flux dialyzer, both Fresenius Medical Care, Bad Homburg, Germany; blood flow (Q_b) and dialysate flow (Q_d) rates 250 mL/min). Dialyzer clearance (CL_{dial}) was calculated from pre- (C_a) and postfilter (C_v) serum drug concentrations: CL_{dial}=plasma perfusion rate (Q_b×(1−hematocrit))× extraction ratio (C_a−C_v)/C_a. Notice adequate myelotoxic reaction (platelets, WBC, and hemoglobin) in response to dosage-reduced oxaliplatin administration and timing of HD treatment (depicted by *gray areas*)

explained by covalent binding of platinum to the polysulfone dialyzer membrane.

In summary, we present first-in-literature experience of long-term oxaliplatin clearance by HD. Similarly to patients with a normal GFR [5], daily dialysis over five consecutive days was able to reduce serum platinum below 50 % of C_{max}. Therefore, we concluded that oxaliplatin clearance by daily HD efficiently reduces platinum levels to non-toxic levels (C_{min} 435 µg/L after 5 days and 273 µg/L after 14 days), which should be incorporated into dose adjustment concepts. Showing a partial response after 3 cycles, we can also conclude antitumoral therapeutic effectiveness.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the patient described.

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