CASE REPORT

Enhanced elimination of cyclophosphamide by high cut-off haemodialysis: single-dose pharmacokinetics in a patient with cast nephropathy

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SUMMARY

High cut-off (HCO) haemodialysis removes free light chains in patients with multiple myeloma. This is possible as HCO dialysers allow clearance of molecules up to a molecular weight of 65 kDa. In contrast, high-flux dialysers, which are used in routine haemodialysis, only remove molecules up to a molecular weight of 20 kDa. Even though patients with advanced myeloma frequently need dialysis and alkylating agents, drug dosing recommendations in this patient population are scarce at best or absent as for cyclophosphamide dosing in patients with myeloma undergoing HCO dialysis. Therefore, we aimed to determine pharmacokinetics of cyclophosphamide in a 52-year-old man (height 172 cm, weight 80 kg) with cast nephropathy. Intermittent 4-hour haemodialysis was started ~6 hours after the end of a 70 min cyclophosphamide infusion containing 1700 mg of this drug. Blood/dialysate flow rates were 300/500 mL/hour, respectively. Peak concentration of cyclophosphamide was 24.7 mg/L. Using HCO dialysis, plasma concentration of cyclophosphamide decreased from 10.8 mg/L to 3.7 mg/L during the treatment. The calculated whole blood dialyser clearance was 166 mL/min. HCO dialysis led to a marked decrease of cyclophosphamide resulting in a a 50% reduction in half-life as compared with the half-life before dialysis. This removal has to be accounted for in dosing cyclophosphamide.

BACKGROUND

High cut-off (HCO) haemodialysis has been introduced to remove large quantities of free light chains in patients with multiple myeloma, improving renal outcome in observational and case–control trials.[1 2] Results of a multicentre prospective trial are eagerly awaited (European trial of free light chain removal by extended haemodialysis in cast nephropathy).[3] HCO dialysers are characterised by a large pore size, allowing enhanced removal of substances with a molecular weight up to 65 kDa, without substantial removal of albumin.[4] Anecdotal reports show an enhanced clearance of drugs by HCO dialysers, so that HCO dialysis can be even used to treat drug overdose.[5 6] Data on dosing cyclophosphamide in patients with myeloma undergoing HCO dialysis are absent.

Therefore, we aimed to investigate the elimination of cyclophosphamide during HCO dialysis, a therapy frequently needed in patients with myeloma with cast nephropathy.

CASE PRESENTATION

A 52-year-old Caucasian man (height 170 cm, weight 80 kg) was admitted to our tertiary care hospital with pneumonia. Aside from clinical and radiological signs of pneumonia, his clinical chemistry results showed a markedly elevated serum creatinine of 9.1 mg/dL (0.73–1.18 mg/dL). As renal impairment was not known, the patient underwent renal biopsy which revealed a light chain cast nephropathy caused by monoclonal kappa light chains. In the blood, kappa light chains were markedly elevated to 7350 mg/L (6.7–22.4 mg/L).

Immunosuppressive treatment with cyclophosphamide, bortezomib and dexamethasone was initiated. To obtain maximum therapeutic levels of cyclophosphamide, we administered a dose of 900 mg/m^2, that is, 100% of the standard dose. In order to minimize side effect of cyclophosphamide and its metabolites, HCO dialysis using an APS–21 EH filter (Asahi, Japan) was started ~6 hours after end of the cyclophosphamide infusion. Blood/dialysate flows were 300/500 mL/min, respectively. Vascular access was obtained by a double-lumen, non-tunnelled dialysis catheter in the right internal jugular vein.

INVESTIGATIONS

Dialyser clearance was calculated from concentrations before (C_{in}) and after (C_{out}) the dialyser as $CL_{dial}=(Fl_{in}\times C_{in}-Flout\times C_{out})/C_{in}$ with plasma flow in (Fl_{in}) and out (Fl_{out}) of the dialyser estimated by blood flow and a haematocrit of 26%. All samples were centrifuged at 1300 g for 10 min at 4°C. Plasma was separated and stored at −80°C until analysis. After fluid extraction (sodium carbonate/diethyl ether) and derivatisation with trifluoroacetic acid anhydride, the amount of cyclophosphamide was quantified by gas chromatography (Agilent GC 7890A) with mass spectrometric detection (Agilent MS 5975C) in the selected ion monitoring mode. Measuring range of cyclophosphamide was 0.005–200 mg/mL with an intra-assay imprecision of 4.5%. For calibration, ifosfamide was used as an internal standard.

OUTCOME AND FOLLOW-UP

Serum peak concentration of cyclophosphamide after the end of the 70 min infusion was 24.7 mg/L. Using HCO dialysis, cyclophosphamide concentration decreased from 10.8 to 3.7 mg/L. The whole

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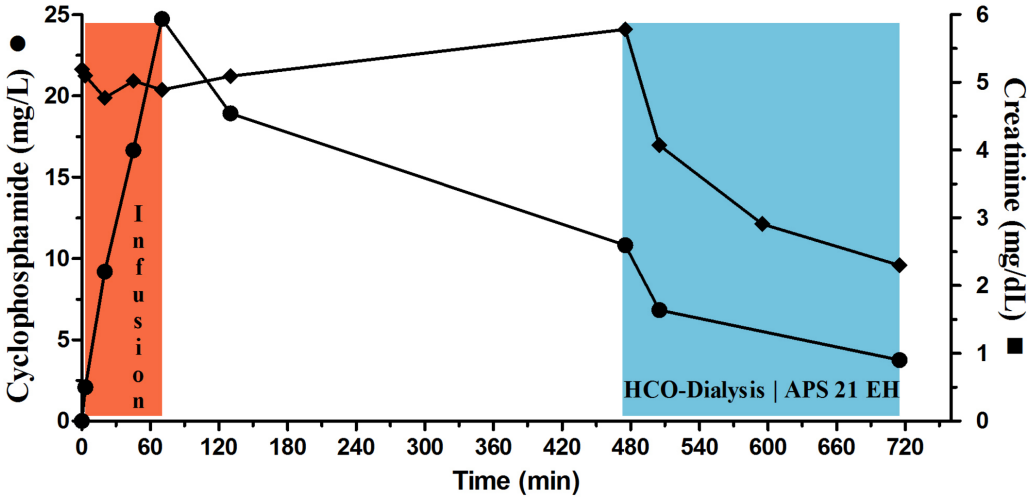

Figure 1 Serum levels of creatinine and cyclophosphamide over time in a patient with cast nephropathy undergoing high cut-off (HCO) dialysis after intravenous administration of cyclophosphamide. Red background represents the time of cyclophosphamide infusion. Blue background represents the time of HCO dialysis.

blood dialyser clearance for cyclophosphamide was 166 mL/min. The plasma dialyser clearance was calculated to be 123 mL/min. Cyclophosphamide plasma half-life of 5.7 hours before HCO dialysis was reduced to 2.62 hours during HCO dialysis (figure 1). After four cycles of chemotherapy and chronic dialysis treatment for 3 months, the patient does currently not require dialysis. Even after an autologous stem cell transplantation 6 months after his first admission, both his serum creatinine of ~1.8 mg/dL and his creatinine clearance ~33 mL/min/1.73 m^2 remain stable.

DISCUSSION

We could show for the first time that HCO dialysis eliminates a considerable amount of cyclophosphamide as evidenced by the decrease in plasma half-life from 5.7 hours before HCO dialysis to 2.6 hours during HCO dialysis. While the elimination half-life without dialysis in our patient is comparable to the half-life of 7.3±3.2 hours in patients with severe renal failure, that is, creatinine clearance of 10–25 mL/min, the half-life during HCO dialysis is about a third of that described previously (7.3±1.8 hours).[7] Despite studying pharmacokinetics of cyclophosphamide in only six patients, it is thus far the largest study even published.[7] Unfortunately, dialyser clearance had not been measured in this study. A study from the 1980s in four chronic haemodialysis patients found a dialyser clearance of 104 mL/min,[8] which was lower than the dialyser clearance we determined in our patient.

What could have contributed to the higher clearance/shorter half-life in our HCO dialysis treated patient? Patients in the study by Haubitz *et al* were dialysed shorter (3–4 hours instead of 4 hours) using a smaller surface area dialyser than ours (1.3 m^2 instead of 1.8 m^2) using a lower blood (200 mL/min instead of 300 mL/min) at that. The time between the end of the cyclophosphamide infusion and the start of the dialysis session was comparable.

Does it make a difference whether one uses a normal polysulfone membrane or an HCO membrane? There are theoretical considerations to believe that this is the case. While cyclophosphamide itself shows almost no protein binding (0%–10%), the alkylating metabolites of cyclophosphamide exhibit a protein binding of >60%.[9] Those might have been removed due to the large pore size of the HCO dialyser. As they are not routinely measured in clinical chemistry laboratories, this reasoning remains speculative but might give rise to future investigations. We assume that the potential removal of those protein bound active metabolites by HCO dialysis might explain why our patient did not show any clinical or laboratory signs of toxicity, especially no leucocytopenia (nadir on day 11 was 4.0×10^3/µL [$4.0–10\times10^3$/µL]), despite receiving the full dose of cyclophosphamide.

Current dosing recommendation advice to reduce the dose of cyclophosphamide up to 50% of the standard dose in dialysis patients. Within the limitation of a case report, our data suggest that this dose reduction could have led to a severe underdosing of cyclophosphamide in our patient, especially if dialysis is scheduled after cyclophosphamide infusion, which is frequently done in acute severe vasculitis patients. Further pharmacokinetic studies in haemato-oncological patients with renal impairment and dialysis dependence are warranted to develop safe but effective dosing strategies of chemotherapeutic agents.

Our anecdotal data suggest that dose adaption of cyclophosphamide in haemodialysis-dependent patients is not necessary if HCO dialysers are employed lag time of 6–8 hours between the

Learning points

- Intermittent haemodialysis with an HCO dialyser that removes light chains in patients with myeloma also eliminates considerable amounts of cyclophosphamide from the bloodstream and might even reduce protein bound alkylating metabolites of cyclophosphamide.
- To avoid disproportionately high side effects (leucocytopenia), it is important to remove the unmetabolised cyclophosphamide from the bloodstream in a timely manner.
- Even in end-stage renal diseases, a full dose of cyclophosphamide may be applied, as efficient elimination by HCO dialysis is feasible.

end of cyclophosphamide infusion and the start of the dialysis session is used.

Contributors GE, CH and JK treated the patient and wrote the manuscript. NK-V measured the cyclophosphamide levels, created the figure and revised the manuscript.

Competing interests None declared.

Patient consent Obtained.

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