Daily postdilutional hemodiafiltration with FX800 polysulfone dialyzers for removing kappa light chains in multiple myeloma-induced kidney injury

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ABSTRACT

Multiple myeloma is an increasing cause of renal failure in the elderly. Early diagnosis of myeloma-associated acute renal failure is paramount and rapid initiation of disease-specific treatments with a combination of chemotherapy and dialytic therapies for instant removal of free light chains have been proposed. For immediate light chain removal, high cut-off dialyzers have been reported to yield superior light chain clearance parameters, but these dialyzers are not widely used due to increased treatment costs. In addition, the clinical virtue of hemodiafiltration (HDF) has not yet been definitively determined. We hereby present the case of a 70-year-old female patient with kappa light chain myeloma and acute on chronic renal failure. Daily HDF for 1-week using standard polysulfone high-flux dialyzers was implemented and led to remarkable and effective light chain reduction ratios between 87% and 95%.

Key words: Multiple myeloma, post-dilutional hemodiafiltration, kappa light-chains, FX 800 dialyzers

Introduction

Multiple myeloma is the second most common form of hematological malignancy after non-Hodgkin lymphoma and represents the hematological disease most often associated with acute kidney injury.[1] Comparable to chronic kidney disease (CKD), it increases with age with a male preponderance. Diagnosis is based on the presence of excessive monoclonal plasma cells in bone marrow, monoclonal immunoglobulins or light chains in serum or urine and related organ or tissue damage such as renal insufficiency, anemia, lytic bone lesions or cardiac and neurological involvement. About 18% of patients present light chain multiple myeloma (LCMM).

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One major cause of renal damage in LCMM is glomerular filtration of immunoglobulin light chains with subsequent overflow proteinuria. The combination of large amounts of monoclonal light chains reabsorbed via the tubules and their unique physicochemical characteristics are responsible for progressive renal damage due to cast nephropathy. Treatment of elderly patients consists of cycles of melphalan and steroids, although new chemotherapy protocols incorporating bortezomib or thalidomide have been reported.[2,3] In patients with severe renal failure, a combination of bortezomib plus dexamethasone has been proposed even in older patients.[4] A major drawback of these regimens is the delayed efficacy in reducing light chain mass and slowing of light chain production rates.

High cut-off dialyzers, e.g. HCO 1100® (Gambro) have been developed for immediate removal of toxic light chains and treatment of renal failure. It is hoped that aggressive urgent light chain removal in combination with chemotherapy will preserve and improve residual renal function, potentially leading to dialysis-independent renal survival and improved patient outcome. Nevertheless, these filters and their treatment-related side-effects, e.g., filter-associated albumin and immunoglobulin losses, are expensive and not routinely available for daily use, except in the setting of clinical studies. Therefore,

we investigated the potential capacity of the standard polysulfone high-flux dialyzer FX800® (Fresenius Medical Care) in removing kappa light chains in a 70-year-old female patient with LCMM and dialysis-dependent acute renal failure.

Case Report

A 70-year-old female with diabetes, osteoporosis, hypertension and atrial fibrillation presented with advanced renal failure, progressive anemia and signs of peripheral polyneuropathy. Due to reversible brachio-facial cerebral ischemia in 2000 and chronic atrial fibrillation, she was on permanent warfarin therapy. On physical examination, she was hypertensive with no overt signs of fluid overload. Retrospective chart analysis revealed a rise in serum creatinine from 1.48 mg/dl (estimated glomerular filtration rate [eGFR] of 35 ml/min/1.73 m^2 body surface area [BSA]) in November 2008 to 5.68 mg/dl (eGFR of 7 ml/min/1.73 m^2 BSA) on admission in February 2010. The patient was anemic but normocalcemic (hemoglobin [Hb] 9.5 g/dl, calcium 2.41 mmol/l). Ultrasound showed normally sized kidneys with increased reflexivity. Serum protein electrophoresis disclosed IgA and IgG deficiency with IgM levels within normal limits. 24 h urine analysis showed a urine volume 850 cc and a proteinuria of 1400 mg/day. Immunofixation of the urine disclosed monoclonal kappa light chains of 2.6 mg/dl. The serum kappa to lambda free light chains (FLC) ratio was calculated at 288, well above proposed normal limits of 0.37–3.1 in patients with acute kidney injury without multiple myeloma. Bone marrow aspiration showed 30–40% infiltration of bone marrow lacunae by typical plasmacytoma cell nests. LCMM expressing kappa light chains was thus diagnosed. X-ray evaluation did not show typical signs of osteolytic lesions but diffuse osteoporosis. Cardiac magnetic resonance imaging could not be performed as the patient had a pacemaker implanted to treat sick-sinus-syndrome but echocardiographic evaluation was in line with a mild form of AL-induced amyloid deposition disease. Due to the therapy with warfarin concomitant with a prolongation in bleeding time and clinically manifest nasal bleeding, a renal biopsy was not performed. To treat renal failure, a double-lumen central vein catheter was placed in the right jugular vein and chronic hemodiafiltration (HDF) was initiated. At the same time, standard chemotherapy with melphalan and dexamethasone with concomitant application of bisphosphonates during each chemotherapy cycle was started. Daily HDF (except on Sunday) was carried out from the 5th to 12th of February 2010, followed by standard thrice weekly HDF therapy. Kappa light chain reduction ratios, as well as different other clearance parameters, were calculated for a total of 13 treatment sessions [Tables 1-3].

Although urgent daily HDF and chemotherapy were started, the patient did not recover renal function on follow-up. Since February 2010, eight cycles of chemotherapy have been given with a total dosage of 70 mg of melphalan. Following the initial therapy, the patient was hemodialyzed 3 times/week. Laboratory analysis was as follows: Creatinine 7.73 mg/dl (eGFR of 6 ml/min/1.73 m^2 BSA), Hb of 12.7 g/dl while on chronic erythropoietin medication (darbepoetin alpha 20 µg/week), calcium 2.34 mmol/l and ß2-microglobulin 17,200 µg/l. Repeat bone marrow aspiration after the fifth cycle of chemotherapy showed a reduction of myeloma infiltration to 10%. After 3 years, the patient died in the immediate postoperative period after suffering from an acute occlusion of the distal aorta (Leriche syndrome).

Discussion

Although LCMM-associated renal damage was not histologically proven, retrospective chart review in conjunction with laboratory data and the past medical history of controlled diabetes and hypertension made light chain associated renal damage due to cast nephropathy most likely. Recent studies have demonstrated the value of determining light chains directly in serum or urine to diagnose myeloma or monitor treatment effects.[5,6] It could be demonstrated that pathologic light chain ratios in 41 patients with multiple myeloma-induced kidney failure are diagnostic of multiple myeloma with a specificity of 99% and a sensitivity of 100% respectively.[7] In myeloma patients, clonal proliferation of plasma cells can result in amounts of FLCs thousands of times higher than normal thus leading to impaired kidney function further deteriorating clearance of FLCs. It has been proposed that the combination of multiple myeloma and acute kidney injury might be treated most successfully as a medical emergency with one cornerstone of therapy being chemotherapy to reduce FLCs production and the other being immediate removal of circulating FLCs via dialytic methods thus increasing chances of dialysis independent renal survival. In 2007, efficient removal of FLCs was described *in vivo* and *in vitro* models applying different filter types as well as filter settings of 2 or 3 in series.[8] In this study, due to extensive treatment schedules, three of five patients with cast nephropathy were reported to be dialysis independent on follow-up but frequent rebound of FLC concentration after refilling was also described. Recently histologically-proven resolution of cast nephropathy in a 61-year-old patient without renal recovery following FLCs removal has been reported. In this

Table 1: Pre- and post-levels of kappa and lambda light chains (mg/l), urea (mg/dl) and β2-microglobulin (µg/l) over the treatment cycle of 13 HDF sessions

Day	1	2	3	4	5	6	7	8	9	10	11	12	13
	Friday	Saturday	Monday	Tuesday	Wednesday	Thursday	Friday	Tuesday	Thursday	Saturday	Monday	Wednesday	Friday
Kappa													
Pretreatment	1445	805	903	1013	1290	1140	1415	1693	2065	1840	2550	2085	2048
Posttreatment	115	99	110	122	174	123	129	122	133	104	156	131	106
Lambda													
Pretreatment	6	6	5	6	4	5	5	5	5	6	6	6	6
Posttreatment	4	3	4	5	5	5	3	5	4	4	4	4	4
Kappa/lambda-ratio													
Pretreatment	258	134	181	169	323	228	283	339	413	307	425	348	341
Posttreatment	29	33	28	24	35	25	43	24	33	26	39	33	27
Urea													
Pretreatment	110	104	116	69	56	45	40	95	38	49	73	68	67
Posttreatment	23	27	25	18	14	9	8	13	8	4	10	15	10
β2-microglobulin													
Pretreatment	9610	5280	12,210	12,650	13,740	14,950	14,590	21,230	18,460	17,960	23,130	22,870	21,330
Posttreatment	3090	3040	4370	4830	5470	3530	3360	4400	3890	3990	4870	5950	4940

HDF: Hemodiafiltration

Table 2: Kappa light chain, β2-microglobulin and urea reduction ratios as well as further relevant treatment associated parameters over the treatment cycle of 13 HDF sessions

	1	2	3	4	5	6	7	8	9	10	11	12	13
	Friday	Saturday	Monday	Tuesday	Wednesday	Thursday	Friday	Tuesday	Thursday	Saturday	Monday	Wednesday	Friday
Kappa-RR	92	88	88	88	87	89	91	93	94	94	94	94	95
β2-RR	68	42	64	62	60	76	77	79	79	78	79	74	77
U-RR	79	74	78	74	75	80	80	86	79	92	86	78	85
UF	400	840	590	482	992	200	300	0	0	0	200	800	0
HDF post	16.6	20.0	12.3	9.3	14.2	28.0	28.8	29.0	32.0	29.6	32.4	24.8	29.5
Blood flow	372	366	365	339	322	400	360	381	400	400	381	325	382
Blood volume	81.5	67.3	74.8	67.9	67.1	84.6	82.5	93.0	93.7	95.2	94.0	82.0	94.3
KtV-urea	1.72	1.49	1.69	1.47	1.54	2.03	1.77	2.23	1.69	2.05	1.82	1.67	2.11
Session time	208	178	199	194	199	212	206	235	234	238	235	237	236

UF: Ultrafiltration in ml, HDF post: Hemodiafiltration volume in l (postdilution), Blood flow: Blood flow pump volume in ml/min, Blood volume: Total processed blood volume per session, session time in minutes, RR: Reduction ratios

Table 3: Statistical data of kappa light chain, β2-microglobulin and urea-RR as well as further relevant treatment associated parameters of all 13 HDF sessions

HDF associated treatment parameters	Mean	Median	Minimum	Maximum	Range	SD
Kappa-RR (%)	91	92	87	95	8	3
β2-RR (%)	70	76	42	79	37	10
Urea-RR (%)	81	79	74	92	18	5
UF (ml)	343	250	0	992	992	337
HDF post (l)	23.9	28.3	9.3	32.4	23.1	7.6
Blood flow (ml/min)	370	377	322	400	78	25
Blood volume (l)	82.8	82.3	67.1	95.2	28.1	10.0
KtV-urea	1.79	1.72	1.47	2.23	0.76	0.23
Session time (min)	215	210	178	238	60	19

UF: Ultrafiltration in ml, HDF post: Hemodiafiltration volume in l (postdilution), Blood flow: Blood flow pump volume in ml/min, Blood volume: Total processed blood volume per session, session time in minutes, RR: Reduction ratios

case, intensive hemodialysis with two high cut-off filters in series had been applied.[9] High cut-off filters, such as the HCO 1100® (Gambro), have a cut-off of roughly 50 kD. Therefore, major drawbacks in their use are, besides high filter costs, treatment-associated costs due to losses of albumin that frequently need to be replaced. The purpose of this case report was to determine the effectiveness of standard postdilutional HDF using an extended treatment regimen with FX800 polysulfone dialyzers in removing kappa FLCs in LCMM. Our data clearly show high reduction ratios for kappa light chains between 87% and 95%. Nevertheless, as reported earlier,[8] we could also find a complete rebound phenomenon on the next day. As we did not measure FLCs during treatment intervals, exact time points when rebound was complete are unclear. In future, these measurements might be useful in determining the value of continuous hemodialysis methods in yielding sustained low FLC levels and thus potentially increasing rates of renal recovery in cast nephropathy. In our patient, extensive treatment over 1-week was followed by standard HDF thrice weekly. Probably due to reducing the treatment frequency (although treatment time was increased), mean FLC concentrations rose about 75% (from a mean 1144 mg/l on daily HDF to 2047 mg/l on thrice weekly HDF) although effects of chemotherapy and residual renal function on changes in tumor generation time and FLC concentration in our nonoliguric patient over the study period cannot be excluded. So far the virtue of postdilutional HDF in removing kappa light chains has not been defined. Correlation analysis between HDF volumes and kappa reduction ratios showed a high correlation coefficient of 0.77 indicative of a relevant clinical benefit of high HDF volumes in the treatment of myeloma-induced acute kidney injury due to cast nephropathy. Nevertheless, it must be mentioned that kappa light chains are more easily removed via filtration than their lambda counterparts because of their lower molecular weight and the lesser likelihood of multimer formation. It is known that multimer light chains can be extracted from blood via adsorption on polymethylmethacrylate membranes without any meaningful removal of lambda FLC in the dialysate.[8] Recently, Oshihara *et al.* also described removal of kappa multimers in chronic end-stage renal disease patients and concluded that in the removal of FLCs via dialysis, not only the light chain isoforms but also potential multimer formation should be considered when determining the best treatment options.[10] Finally, we feel that HDF has very few contraindications. As all hemodialytic procedures, major bleeding complications due to heparin administration have to be considered. In such cases, regional citrate anticoagulation might be applied. In addition, daily HDF in patients with LCMM is not helpful in cases, where renal biopsy has excluded cast nephropathy. In patients, where renal biopsy cannot be performed, HDF might be questioned if ultrasonography shows small kidneys bilaterally indicating only little chances to rescue relevant amounts of renal parenchyma.

Conclusion

We could demonstrate that postdilutional HDF with FX800 polysulfone dialyzers is highly effective in removing kappa light chains in patients with multiple myeloma-induced kidney failure. Daily HDF and most presumably other intermittent dialysis schedules most likely do not prevent high rebound rates thus raising the question of a potential virtue of continuous dialysis modes in the urgent treatment phase until chemotherapy-induced tumor regression is effective.

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