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Long Hemodialysis Treatment with High Cut Off Membranes in Patients with Acute Kidney Injury Secondary to Multiple Myeloma: Case Presentations

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Abstract

Introduction: Multiple Myeloma (MM) as a malignant proliferation of plasma cells in the bone marrow, with an excessive release of serum Free Light Chains (FLC) can be associated with Acute Kidney Injury (AKI). The key to treating AKI is rapid FLC reduction using newer chemotherapeutic agents, such as bortezomib and extracorporeal removal of FLC by using a High Cut Off membranes (HCO) with high permeability and molecular weight cut-off pore size (45-60 kD) for Hemodialysis (HD).

Case Series: We report on four cases with MM who developed AKI and were treated with HCO-HD and specific chemotherapy with bortezomib on our clinic. Initially, 7-h sessions were performed using a 2.1 m^2 HCO filter. Then, it was continued alternately every other day with additional sessions of 8 h.

Results: The mean Reduction Ratio (mRR) of kFLC of the first patient was 49%, 45.5%, mRR of λFLC of the second, 49% of the third, and 60% of the fourth patient, respectively, with the mean value of 50.8%. In the two cases with λFLC the mRR was 52.75% (range 45.5-60%), and in the two other cases with kFLC, the mRR was 49% (with no range variety). Three out of four patients sufficiently recovered the renal function becoming independent of HD.

Conclusion: The combined treatments of chemotherapy plus long HCO-HD sessions are effective in reducing the levels of FLC and sufficiently recovering renal function, allowing significant savings, better quality of life and longer life span.

Keywords: Acute kidney injury; Multiple myeloma; High-cut off membrane dialysis

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Introduction

Multiple Myeloma (MM) is characterized by a malignant proliferation of plasma cells in the bone marrow, and significant volume release of serum- Free Light Chains (FLC), causing an Acute Kidney Injury (AKI) due to an intratubular precipitation and development of cast nephropathy [1].

As a result of the FLC deposition along with the Tamm-Horsfall protein, there is cast formations in the distal tubules that cause renal failure in these patients.

FLC can be classified into two main types: kappa (κ) and lambda (λ). κ FLC have a molecular weight approximately of 22.5 kDa and a monomeric form- meaning they exist as single molecules, and λ FLC have a molecular weight of approximately 45 kDa and dimeric form- meaning they exist as pairs of molecules [2].

According to the International Myeloma Working Group (IMWG) renal impairment criteria: Serum Creatinine levels (sCr) >2 mg/dl or 176 umol/l and e GFR <40 ml/min/1.73m^2, it has been reported that around 20% to 30% of cases had some kind of kidney injury at the time of diagnosis, with only 10% of them requiring hemodialysis [3].

The renal impairment caused by cast nephropathy can lead to a higher risk of mortality and such patients have a decreased one-year survival compared to those without kidney involvement [4]. Recovery of the kidney function is a better predictor of survival than just a hematologic response to chemotherapy [4,5]. This means that patients who experience improvement in kidney function tend

to have better overall outcomes, even if their hematologic response is not so strong.

The cornerstone of managing myeloma cast nephropathy is rapid reduction in FLC. There are three main treatment modalities for the acute renal failure:

1. Supportive care helps eliminating the causes for aggravation of nephrotoxicity and cast formation. It can be achieved by adequate fluid intake to maintain kidney perfusion and help flush out light chains, proper correction of hypercalcemia, avoidance of nephrotoxic agents and managing infections [6].

2. Reduction of FLC production that is achieved by the use of combined regime with: Proteasome inhibitors drugs (bortezomib, carflizomib and ixazomib), Immunomodulatory Drugs (IMiDs), (thalidomide, lenalidomide, and pomalidomide) and corticosteroids [7-9].

Newer chemotherapeutic agents such as: bortezomib, thalidomide, and lenalidomide have the ability to rapidly lower or reduce the levels of FLC in the blood, which are considered the primary culprits of causing renal damage in the multiple myeloma [7]. Bortezomib as a proteasome inhibitor rapidly lowers FLC by inhibiting plasma cell proliferation, inhibits the breakdown of inhibitory kappa B and consequently stabilizes the NFκB complex. NF-κB plays a central role in the pathogenesis of multiple myeloma and is associated with acute kidney injury and development of Interstitial Fibrosis and Tubular Atrophy (IFTA) [9]. Because of the response achieved with bortezomib in the acute kidney injury, it has been labeled as "renoprotective" chemotherapy [10].

3. Extracorporeal therapies for elimination or reduction of the circulating FLC are plasmapheresis, conventional High Flux (HF) dialyzers and long hemodialysis sessions with High Cut-Off Filters (HCO- HD) [11]. It is considered that PF and HF hemodialysis are less effective than the removal performed by long HCO-HD sessions [9,12]. This difference appears to be due to a longer duration of the HCO-HD sessions and better elimination of increased FLC levels as a result of their intercompartmental redistribution from the extra to the intravascular compartment and their prompt reduction [13].

HCO membranes have a large pore (cut-off of 45-60 kD), allowing the filtration of both kappa (k) and lambda (λ) FLC [2,12].

Case Series

We report four cases with MM who developed AKI and were treated with dialysis using HCO membranes and specific chemotherapy with bortezomib at our clinic.

Case 1

A 74-year-old patient was referred to our clinic, due to anuria, malaise and elevated levels of serum urea and creatinine. The patient was previously diagnosed with MM in 2005, and was treated with four cycles of chemotherapy with Cyclophosphamide, Thalidomide, Dexamethasone (CTD) protocol and autologous bone marrow transplantation. Afterwards it was followed by a long remission of the disease. During a routine hematological check-up, he complained of a lower back pain and malaise. Additional analyses revealed the presence of Bence Jones proteins in urine. MRI of the spine showed changes from the previously confirmed MM and infiltration at the level of L2 and L3 vertebral bodies of the vertebral column, highly suspicious for recurrence of the disease and a biopsy of the change was done. Also, a sternal puncture was performed, both confirming the recurrence of MM.

At the admission elevated serum Creatinine (sCr) 676 umol/l and urea 50 mmol/l with hyperkalemia 8.3 mmol/l were detected, uric acid 650 umol/l, LDH 588 U/l, IgA 5.9 g/l, proteinuria 0.45 g/l, κ FLC 1770 mg/l, λ FLC 11.7 mg/l, ↑FLCs k/λ 152.

On the first day of admission, an urgent HD was performed with simultaneous hydration. After the initial HD, regular HD with Medium Cut off (MCO) membranes were performed. In the following days, in consultation with the hematologist, chemotherapeutical treatment was initiated according to the VTD protocol (bortezomib, thalidomide, dexamethasone), and we proceed with hemodialysis with HCO membranes, with large pores and permeability. A total of six hemodialysis treatments lasting 7 h to 8 h were performed using a 2.1 m^2 HCO filter. After the HCO-HD sessions combined with the specific chemotherapy, there was a significant decrease in degradation products, and drop in serum values of FLC, with an improved diuresis of 4100 ml, that gradually normalized polyuria phase up to 2500 ml. Thus, it was an indication to stop with HD treatment.

Case 2

A 68-year-old female, came to us, after developing AKI, with already initiated HD with conventional HF-dialyzers in another nephrology institution. Due to a history of prolonged lumbar pain, albumin/globulin dissociation, craniogram with smaller, diffuse, round and clearly limited osteolytic lesions the patient was referred to the hematologist. Several additional investigations were made and MM was diagnosed. The values of FLC at the time of the diagnosis were: κ FLC 35 mg/l, λ FLC 2420 mg/l, FLCk/ λ 0.0148. Abdominal ultrasound showed kidneys with regular shape and echogenicity, cystic secondary deposit in the liver and an ovarian cystic formation highly suspicious for an ovarian cystadenocarcinoma. Sternal puncture showed infiltration of bone marrow over 80% with plasma cells confirming the MM diagnosis. Immediate treatment according to the VTD protocol was initiated and she was referred to our clinic. At the time of admission laboratory findings were: sCr 693 umol/l, urea 15 mmol/l, K 4.5 mmol/l; Ca 2.7 mmol/l, IgG 55.7, total proteins 97 mg/l, albumins 23 mg/l, κ FLC 35 mg/l, λ FLC 2420 mg/l, FLC k/ λ 0.0148, LDH 639 U/l, CRP 9.8 mg/l, Hgb 75 g/l. Five HCO-HD sessions were performed, followed by a corresponding drop in FLC, but without a corresponding decrease of the values of degradation products. Therefore, the MCO-HD and specific chemotherapy were continued, but unfortunately, the patient did not recover the kidney function.

Case 3

A 59-year-old male was admitted at our clinic due to elevated values of degradation products sUr 23 mmol/l, sCr 1042 umol/l, anuria and findings of bicytopenia Er 2.1 × 10^{12}/l and Tr 68 × 10^9/l from the blood count. Treatment with conventional HF-HD was started. In the meantime, due to anemia, thrombocytopenia, hypercalcemia, albumin-globulin dissociation, pain in the lumbosacral region and positive Bence-Jones protein in urine, a hematologist was consulted and additional examinations were required. Laboratory findings showed: IgA - 30.8 g/L, κ FLC 10,900 mg/l, λ FLC 580 mg/l, FLC k/ λ 18, albumin 34 g/l, globulin 57 g/l, total proteins 91 g/l. Ca 2.5 mmol/l and sternal puncture showed infiltration of bone marrow over 75% with plasma cells and finding in addition to MM. Treatment with specific chemotherapy according to VTD protocol was initiated and

four sessions of HCO-HD were performed, which lead to a decrease of: FLC levels, sCr, sUr and hypercalcemia, with an improved diuretic response and kidney function, without a need for further HCO-HD treatment.

Case 4

A 72-year was admitted at our clinic due to an increase in serum degradation products, sCr 420 umol/l, sUr 20 mmol/l, Hgb 92 g/l, K 5.7 mmol/l, following the performed CT urography due to cystic changes in the kidneys noted on echosonography of the urinary tract. CT urography showed a polylobulated contour of both kidneys, bilateral blur and edema during delineation of the cortex and medulla, no cystic changes on the right kidney, on the left there was a medullary cyst in the middle parts with diameter 11 mm × 8 mm and another lower one with a diameter of up to 15 mm, and a frontal cortical cyst 12 mm with a denser content in the lower pole. Due to an acute increase in degradation products in the blood, a renal biopsy was performed and the findings were in favor of cast nephropathy. Treatment with HF-HD was commenced. Due to the finding on the renal biopsy, bicytopenia, malaise, and lower back pain, the hematologist was consulted and sternal puncture was made with a plasma cell infiltration over 70% and κ FLC 24 mg/l, λ FLC 10,399 mg/l, FLCk/ λ 0.002 and MM was diagnosed. Treatment with specific chemotherapy was started according to VTD protocol and a simultaneous treatment with HCO-HD. A satisfactory decrease in the degradation products was achieved, with a drop in sFLCs and an adequate diuretic response, with discontinuation of HD treatment.

The dialysis membrane used in all cases was HCO membrane 2.1 m^2. Dialysis was performed daily for a three-day period, then every other day, until the sufficient drop of FLC levels in the blood, below 500 mg/l or kidney function improvement to the point that dialysis may be discontinued. The first HD was conducted for 7 h, and the others up to 8 h, with a blood flow of 250 ml/min to 300 ml/min dialysate flow rate of 500 ml/min. As anticoagulant therapy unfractionated heparin or Low Molecular Weight Heparin (LMWH) was used. Every 2 h, blood count, electrolytes and protein status were analyzed. Concerning the risk of albumin loss, substitution with two or three 50 ml vials of 20% human albumin before the end of each HCO-HD was done. Other supplements, such as calcium gluconate, magnesium sulphate, potassium chloride and epoetin beta were also used. As vascular access we used temporary central venous catheters, which were sealed with 1% sodium heparin. All cases had HBV, HCV and HIV negative serology at the start of dialysis and a signed informed consent form for the insertion of vascular access and another one for the hemodialysis treatment.

Results

In a 20 months period (October 2021 - May 2023), four patients at our clinic were diagnosed with AKI secondary to MM and treated simultaneously with long hemodialysis sessions with HCO membranes and specific chemotherapy.

Three of them were males and one female, with an average age of 68.25 ± 6.65 years. The number of patients with k FLC was equal to those with λ FLC, two in each case. Kidney biopsy was performed only in one case and showed cast nephropathy. Regarding the percent of bone marrow infiltration with plasma cells, the first patient had 82%, the second 80%, the third 75%, and the fourth 70%, with a mean value of 76.75%, respectively. In all four cases, after establishing the diagnosis of AKI secondary to MM, in consultation with a hematologist, specific chemotherapy was initiated according to the VTD protocol. We performed a total of 19 long dialysis sessions with HCO membranes, with a mean value 4.75 ± 0.95 (Table 1, 2).

All four patients achieved FLC levels less than 500 mg/l, but only three patients recovered their kidney function and continued without hemodialysis (Table 2). The mean FLC level at start, before treatment was 6312 ± 4967 mg/l (range 10,900-1630 mg/l). The mean FLC level at the end was 200 ± 161.66 mg/l (range 390-13 mg/l). The percentage of removal of FLC from the beginning to the end of treatment was 86% (range 81.5-98%). The mean Reduction Ratio (mRR) of k FLC of the first patient was 49%, 45.5%, mRR of λ FLC of the second, 49% of the third, and 60% of the fourth patient, respectively, with the mean value of 50.8%. In the two cases with λ FLC the mean removal was 52.75% (range 45.5-60%), and in the two other cases with k FLC, the mean removal was 49% (with no range variety) (Table 2).

The mean sCr level in the 3 patients who recovered their kidney function before treatment was 707.7 umol/l (range 420-1042 umol/l) and 423 umol/l (range 325-555 umol/l), at the end of treatment, respectively. The mean sCr level after three months of follow up was 115 umol/l (range 92-136 umol/l).

We also monitored the kidney function using estimated

Table 1: Personal data, kidney biopsy, number of dialysis sessions, symptoms, chain type, treatment, bone marrow infiltration.

Patient	Gender	Age	Kidney biopsy	No. HCO- HD	Symptoms	FLC Type	Chemotherapy	% of bone marrow infiltration
1	M	74	ND	6	Lumbar pain; Relapse	kappa	VTD	82%
2	F	68	ND	5	Lumbar pain	lambda	VTD	80%
3	M	59	ND	4	Lumbar pain + Sg	kappa	VTD	75%
4	M	72	CN	4	Sg, malaise	lambda	VTD	70%

HCO: High Cut Off; FLC: Free Light Chain; CN: Cast Nephropathy; ND: Not Done; Sg: General Syndrome; VTD: Bortezomib, Thalidomide, Dexamethasone

Table 2: Changes in FLC at start, end, % of removal, type of light chain.

Patient	No of HCO-HD	FLC-start (mg/l)	FLC-end (mg/l)	m RR (%) by HD sessions	Rem. of FLC start- end (%)	FLC Type	FLC 3 months (mg/l)
1	6	1,630	300	49	81.5	k	361
2	5	2,420	390	45.5	83	λ	HDP
3	4	10,900	13	49	81.5	K	12
4	4	10,300	200	60	98	λ	848
Mean	4.75	6,312	451.5	50.8	86	50/50	407

HCO-HD: High Cut-Off Hemodialysis; FLC: Free Light Chain; m RR: mean Reduction Ratio

Table 3: Changes in creatinine and GFR in patients with AKI secondary to MM treated with HCO filters.

Patient	s Cr start umol/l	s Cr end umol/l	s Cr 3 months umol/l	GFR start ml/min/1.73 m^2	GFR end ml/min/1.73 m^2	GFR 3 months ml/min/1.73 m^2
1	676	353	92	7	15	75
2	693	462	HDP	5	8	HDP
3	1042	555	117	4	10	62
4	420	325	136	12	17	48
Mean	707,7	423	115	7	12.5	61.6

HCO: High Cut Off; FLC: Free Light Chain; CN: Cast Nephropathy; ND: Not Done; Sg: General Syndrome; VTD: Bortezomib, Thalidomide, Dexamethasone

Table 4: Changes in albumin in patients with AKI secondary to MM treated with HCO filters.

Patient	Albumin- start (g/l)	Albumin-end (g/l)	Albumin- 1st week (g/l)	Albumin 3 months (g/L)
1	28	35	31	43
2	25	34	28	HDP
3	34	33	30	38
4	47	30	38	5o
Mean	33.5	33	31.75	43.66

AKI: Acute Kidney Injury; HCO: High Cut-Off filters; HDP: Periodic Hemodialysis; MM: Multiple Myeloma

Glomerular Filtration Rate (eGFR) obtained by: Chronic Kidney Disease Epidemiology Collaboration- CKD-EPI 2021 equation. Before hemodialysis treatment with HCO, the mean eGFR was 7 ml/min/1.73m^2 (range 4-12 ml/min/1.73m^2). After treatment, the mean eGFR was 12.5 ml/min/1.73m^2 (range 8-15 ml/min/1.73m^2). The mean eGFR of the three patients who responded to the combination treatment of chemotherapy plus HCO-filter dialysis increased from 14 ml/min/1.73m^2 to 61.6 ml/min/1.73m^2 (range 48-75 ml/min/1.73m^2) at the end of HCO- HD sessions and at three months after the recovery, respectively (Table 3).

Due to the possibility of protein loss, patients were substituted with two 50 ml vials of 20% human albumin before the end of each dialysis session. The data of the serum albumin values at the start, after the first week, at the end of the treatments and three months later are presented in Table 4.

Discussion

We have presented our experience of four patients who had AKI secondary to MM, and were diagnosed and treated at our clinic, in one of them the performed renal biopsy showed histopathological findings of cast nephropathy. The combined treatment of chemotherapy, using VTD protocol and dialysis with HCO membranes proved to be effective and achieved a recovery rate of 75% (three out of four patients), which allowed patients discontinuation of hemodialysis.

Hutchinson et al. showed that in a series of 19 patients with MM and AKI, recovery of kidney function and dialysis free achievement was seen in 14 (74%) of cases after chemotherapy and HCO-HD, that is in line with our findings. As far as specific chemotherapy is concern only 58% of the patients were treated with bortezomib [12]. Sinisalo et al. instituted bortezomib-based therapy as early as possible, usually by the third HCO-HD session, no serious dialysis related complication occurred and six out of seven patients became free of dialysis [14]. Another study showed that sixteen patients (76%) out of 21, became dialysis independent, and 48% had a decrease in their sCr levels below the threshold of 176 umol/l (2 mg/dl) [15].

According to our experience, second case did not achieve recovery of renal function, most likely due to the λ FLC, which are considered to be larger in size and more difficult to eliminate, but also due to the delayed period of diagnosis and already started treatment with hemodialysis at the time of diagnosis, the later initiation of the specific chemotherapy and HCO-HD, and most probably due to the additional malignancy of the ovary and secondary liver deposits. Unfortunately, she died 15 months after the diagnosis of MM and initiation of dialysis treatment. In a case series of five patients, four were with λ FLC and three of the cases had a good response to treatment, with a sufficient recovery of renal function, except in one case, in whom recovery was not complete, probably due to the longer duration of the disease before the beginning of HCO-HD [16]. Conversely, some authors have found equivocal efficacy in the removal of the two types of chains [17]. According to Chang et al. patients with MM who underwent HD demonstrated a significantly decreased survival in the first year following diagnosis in comparison with those without HD [18]. As a limitation we had a small sample size, without possibility to correlate the baseline prognostic characteristics of hematologic and renal response and clinical outcomes.

In contrast to Berni Wennekers et al. study where a total of 151 HCO-HD sessions were performed with an average of 11.6 sessions per patient, the average number of days from the onset of acute renal failure until the initiation of hemodialysis with HCO filter was 27.3 days (range 0-90 days). The average delay was shorter (24.5 days) in those who had recovered their kidney function, compared to 34 who did not [19]. We performed a total of 19 long dialysis sessions with HCO membranes, with a mean value 4.75 ± 0.95 per patient, and the average number of days from the onset of AKI until the start of HCO-HD was 8.5 days, with a range of 2 to 12 days (Table 1, 2). We hypothesize that an early diagnosis and initiation of simultaneous treatment with HCO-HD and specific chemotherapy is the most important for a rapid recovery of renal function and cessation of treatment with HD thereafter. It allows reducing of the burden on the health care system and utilization of health care staff and resources.

We succeed with the mRR% of FLC by the HCO-HD sessions per patient of 50.8% (range 40.5-60%), and the removal of FLC from start till the end of 86% (range 82.5-98%) that is similar with another two-case series with the mRR% by dialysis of 53% to 57% in first one and 58% in the second one [19,20] with final removal of FLC of 93% [19]. In this regard, the main difference between MYRE and EuLite randomized controlled trials was that HCO hemodialysis vs. conventional high-flux HD, turned out to be with a hemodialysis

independence rate at the sixth month of 56.5% (n=26) *vs.* 35.4% (n=17), respectively [20].

Albumin levels can be lowered, hence we infused two vials of human albumin 20% towards the end of dialysis helping to maintain acceptable levels, with a mean of 31.75 ± 4.3 mg/l at the seventh day of treatment sessions compared to 33.5 ± 9.7 mg/l at the start. By the end of the treatment, albumin levels had improved, with a mean of 33 ± 2.1 g/l. Three months after the end of treatment, patients had normal levels of albumin 43.6 ± 4.9 g/l; Bridoux et al. showed that albumin had mean of 31 g/l, after the seventh day of treatment 29.4 g/l, but at the end of treatment, albumin levels had improved, with a mean of 31 g/l, and three months later, after the treatment, patients had normal level of 43.6 g/l [20].

Conclusion

In MM patients presenting with AKI, an early diagnosis and initiation of simultaneous treatment with HCO-HD and specific chemotherapy are crucial for a rapid recovery of renal function and cessation of treatment with HD thereafter. It allows reducing of the burden on the health care system and utilization of health care staff and resources. Dialysis free regimen in such patients allows significant savings, better clinical outcomes, quality of life and longer life span.

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