Hemodiafiltration with ultrafiltrate regeneration reduces free light chains without albumin loss in multiple myeloma patients.

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Abstract
Background Acute kidney injury (AKI) occurs in 12-20% of multiple myeloma (MM) patients. Several studies have shown a reduction of free light chains (FLC) using hemodialysis with High-Cut-Off membranes. However, this technique entails albumin loss. Hemodiafiltration with ultrafiltrate regeneration is a technique that includes a process of adsorption. The aim of this study was to evaluate the effectiveness of hemodiafiltration with ultrafiltrate regeneration in reducing FLC levels without causing albumin loss.

Methods This is an observational study (2012 to 2018) including eleven patients with MM (6 kappa, 5 lambda) and AKI. All patients were treated with chemotherapy and hemodiafiltration with ultrafiltrate regeneration. Blood Samples (pre and post-dialysis) and ultrafiltrate were collected pre and post-resin at 5 minutes after initiation of the session and 5 minutes before the end of the procedure.

Results The serum levels of kappa and lambda were reduced by a 53±14% and 33±22% respectively. Serum albumin concentration remained unchanged after the procedure. In the ultrafiltrate, the mean FLC reduction ratio shortly after initiation of the dialysis procedure was: 99.2% and 97.06% for kappa and lambda respectively, and only 0.7% for albumin; and at the end of the session the percent reduction was: 63.7% and 33.62% for kappa and lambda respectively, and 0.015% for albumin.

Patients clinical outcome was: 36.4% recovered renal function, 18.2% died during the first year and 45.45% required maintenance dialysis.

Conclusions Hemodiafiltration with ultrafiltrate regeneration reduces FLC levels without producing a significant loss of albumin; and, FLC removal is maintained throughout the session. Therefore, hemodiafiltration with ultrafiltrate regeneration may be considered an effective adjunctive therapy in patients with MM.

Background
Multiple myeloma (MM) is a malignant plasma cell proliferation characterized by overproduction of immunoglobulins. Severe acute kidney failure (AKI) is observed in 12-20% of MM patients and it is produced by deposition of light chains, cast formation and tubular obstruction (myeloma cast nephropathy) [1, 2]. Despite improvements in the management of this disease, renal failure remains
an important burden that worsens the prognosis [3] and dialysis is required in a 10% of cases [1, 4, 5].

The objective of MM treatment is to eliminate the production of free light chains (FLC) using chemotherapy (dexamethasone, bortezomib, melphalan, thalidomide, lenalidomide, cyclophosphamide) associated or not to autotransplantation of hematopoietic cells [6]. An adjuvant therapy is the use of extrarenal depuration techniques to reduce the levels of FLC so the renal damage is minimized. In recent years, several studies have been published on the effectiveness of very high permeability, “High-Cut-Off” (HCO) membranes for the removal of FLC and protein bound uremic toxins [7]. Kappa and lambda FLC have a molecular weight of 22.5 kD and 45 kD, respectively. The HCO membranes have a large pore (cut-off of 45-60 kD), allowing the filtration of both FLC [5, 8, 9]. The removal of FLC with this membrane is 66-69% of kappa and 71-90% of lambda [10, 11]. The procedure is more effective if applied promptly after an early diagnosis and treatment of the MM [5, 12]. With a sustained reduction of FLC the renal recovery is as high as 64% [10, 13, 14]. It has been reported a relationship between early treatment and the renal recovery and with a better survival [15]. An important drawback of this procedure is the undesirable loss of albumin that may require its replacement [6, 10]. Furthermore, in a recent randomized clinical trial involving 98 patients with myeloma cast nephropathy on chemotherapy, the use of HCO hemodialysis compared with conventional hemodialysis did not result in a significant benefit with respect to hemodialysis dependence at 3 months [16]. Later, Hutchison et al. shown that HCO hemodialysis was not associated with an improvement in renal recovery as compared with High Flux- hemodialysis in patients with a new diagnosis of MM and myeloma cast nephropathy who received modified-dose bortezomib-containing chemotherapy although in both groups there was a sustained early reduction in serum FLC levels[17].

Hemodiafiltration with regeneration of the ultrafiltrate by adsorption using a resin has been introduced as an extrarenal clearance technique that combines convection, adsorption and diffusion. It uses a “Super High Flux” polyphenylene membrane with a cut-off of 42 kD. Our group has reported that hemodiafiltration with ultrafiltrate regeneration, may improve uremic protein-bound toxin
removal, inflammatory state, endothelial damage, and oxidative stress relative to on-line hemodiafiltration and high-flux hemodialysis [18]. Since a cut-off of 42 kD should allow the passage of FLC (especially kappa), without the loss of albumin (molecular weight 55-60 kD), hemodiafiltration with ultrafiltrate regeneration might be a reasonable strategy for FLC removal, thus it could be used as an adjuvant treatment to the MM chemotherapy. Testa et al. showed that this technique removes FLC, particularly kappa, in patients with both monoclonal and polyclonal gammopathies [19]. In a preliminary work we had explored the feasibility of using hemodiafiltration with ultrafiltrate regeneration in 3 patients with MM and AKI, the results were encouraging among other reasons because there was no need for albumin replacement [20]. Now, our aim is to evaluate the effectiveness of hemodiafiltration with ultrafiltrate regeneration in reducing FLC and its effect on albumin in patients with AKI secondary to MM.

Methods

Patients

This is an observational study that includes 11 patients with AKI due to MM diagnosed in our centre between July 2012 and December 2018. All patients were immediately treated with chemotherapy according to Hematology protocol (based on bortezomib and corticosteroids) and hemodiafiltration with ultrafiltrate regeneration was used as renal replacement therapy. All patients started on hemodiafiltration with ultrafiltrate regeneration. The main criteria for renal replacement therapy was a decreased glomerular filtration (<7-10 ml/min/1.73m²). The baseline creatinine before diagnosis of MM was normal. All patients were followed until death or censored at 2019 January 31st if still alive. The diagnosis of MM was made based on the presence of clonal bone marrow plasma cells (>10%), serum and/or urinary monoclonal protein and evidence of end organ damage that can be attributed to a plasma cell proliferative disorder [21].

The procedure used to reduce the circulating levels of FLC was the hemodiafiltration with ultrafiltrate regeneration (HFR-SUPRA) (Bellco©/Medtronic©). This technique combines convection, adsorption and diffusion; this is accomplished by two filters and a cartridge. The convection process takes place in the first filter, a Super High Flux polyphenylene membrane with 42 kD cut-off and a 0.7 m² surface.
The generated ultrafiltrate (UF) circulates throughout a cartridge of adsorbent resin (Suprasorb, 80 ml) at a maximum flow rate of 70 ml/min, to remove the uremic toxins from the UF. The UF is subsequently reinfused before it reaches a second chamber containing a low permeability polyphenylene filter of 1.7 m² surface, where the diffusion process takes place. A scheme of the procedure is shown in the Fig 1.

Blood and dialysate flow were set at 300-350 and 500 ml/min respectively. The ultrafiltration rate changed according to interdialysis weight gain. The dialysate calcium and potassium concentration were 3 and 2 mEq/L respectively. The number of hemodiafiltration with ultrafiltrate regeneration sessions was individually adjusted in each case. The duration of the 2 initial dialysis sessions was 150 and 180 minutes respectively, the remaining sessions 240 minutes three times a week. Anticoagulation was achieved by initial bolus of heparin sodium and an hourly dose. A temporary catheter was placed as an initial vascular access and, after two weeks of treatment, it was replaced by a tunneled catheter. Treatment with hemodiafiltration with ultrafiltrate regeneration was extended while the patient required dialysis, even if the serum light chains levels were less than 500 mg/L. An average of 39 ± 28 sessions per patient were performed.

Laboratory tests

Blood samples were obtained from the blood lines pre- and post- filters at the beginning and at the end of the procedure. Samples of UF were drawn before and after the resin cartridge, 5 minutes after the initiation and 5 minutes before the completion of the procedure (Fig 1). The concentration of FLC and albumin were measured in each sample. The serum levels post-dialysis were corrected by the ultrafiltration rate in each case. The extractions were always obtained in the first weekly dialysis. The samples were stored until measurements of FLC below 500 mg/L were obtained.

Albumin was measured by the bromocresol purple colorimetric enzymatic method. The quantification of kappa and lambda FLC in blood and UF samples was performed with the Freelite kit (The Binding Site Group Ltd.) for use in the Siemens BN® II nephelometer; this is a test validated for renal failure patients [22]. The normal range is 3.3 – 19.4 mg/L for kappa and 5.71 – 26.3 mg/L for lambda.

The reduction ratio per session (RRs) was calculated as follows:
RRs = \( \frac{C_{\text{pre}} - C_{\text{post-corr}}}{C_{\text{pre}}} \times 100 \)

where \( C_{\text{pre}} \) is the pre-dialysis concentration and \( C_{\text{post-corr}} \) is the post-dialysis concentration corrected for hemoconcentration according to the following formula:

\[ C_{\text{post-corr}} = C_{\text{post}} / (1 + (\Delta BW / (0.2 \times BW_{\text{post}}))) \]

where \( C_{\text{post}} \) is the post-dialysis concentration without correction, \( \Delta BW \) is the weight reduction during dialysis (ultrafiltration) and \( BW_{\text{post}} \) is the body weight post dialysis [23].

**Statistical Analysis**

Continuous variables are shown as mean (± standard deviation, SD). Categorical variables are presented as percent (%). A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS statistical program (SPSS Inc., Chicago, IL, USA).

**Results**

There were eleven patients with AKI secondary to MM included in the study. All patients were treated early after diagnosis, with hemodialfiltration and ultrafiltrate regeneration. Clinical and demographic characteristics are shown in Table 1.

| Patient | Age (years) | Gender | FLC type | FLC levels at the diagnosis of MM (mg/L) | Serum Creatinine concentration at the diagnosis of MM (mmol/L) |
|---------|-------------|--------|----------|----------------------------------------|----------------------------------------------------------|
| 1       | 64          | F      | κ        | 18806                                  | 0.62                                                     |
| 2       | 52          | F      | κ        | 6178                                   | 1.17                                                     |
| 3       | 75          | F      | λ        | 826                                    | 0.81                                                     |
| 4       | 72          | M      | κ        | 11200                                  | 0.97                                                     |
| 5       | 74          | M      | λ        | 1800                                   | 0.75                                                     |
| 6       | 78          | M      | λ        | 379                                    | 0.23                                                     |
| 7       | 64          | M      | λ        | 569                                    | 0.99                                                     |
| 8       | 85          | F      | κ        | 28023                                  | 0.56                                                     |
| 9       | 76          | M      | κ        | 5243                                   | 0.61                                                     |
| 10      | 65          | F      | λ        | 5852                                   | 0.28                                                     |
| 11      | 75          | M      | κ        | 466                                    | 0.23                                                     |
| **MEAN:**| **71**      | **5F / 6M** | **6κ / 5λ** | **11653 (κ)** | **1885 (λ)**  |

Legend: FLC: free light chain; MM: multiple myeloma; κ: Kappa; λ: Lambda; F: female; M: male.

All patients were caucasian (6 males and 5 females), mean age: 71±9 years with a mean serum creatinine of 0.66 ± 0.31 mmol/L. The serum FLC levels were quantified at diagnosis: kappa FLC
isotype was present in 6 patients (54.5%) and lambda FLC isotype in 5 patients (45.5%). The mean concentration of light chain kappa was 11,653 ± 10,154 mg/L and the mean concentration of light chain lambda was 1,885 ± 2,284 mg/L. The initial levels of FLC and the mean percent reduction of FLC in each patient are listed in Table 1 and 2.

Table 2. Data on treatment and clinical evolution at first year.

| Patient | Onset of HFR since diagnosis (days) | Onset of QT since diagnosis (days) | Mean FLC reduction (%) | Mean Albumin levels pre dialysis (mmol/L) | Mean Albumin levels post dialysis (mmol/L) | Renal recovery |
|---------|------------------------------------|-----------------------------------|------------------------|------------------------------------------|------------------------------------------|---------------|
| 1       | 0                                  | 0                                 | 63                     | 0.52                                     | 0.53                                     | No            |
| 2       | 0                                  | 0                                 | 72                     | 0.37                                     | 0.35                                     | Yes           |
| 3       | 3                                  | 7                                 | 24                     | -                                        | -                                        | Yes           |
| 4       | 0                                  | 4                                 | 54                     | 0.43                                     | 0.40                                     | Yes           |
| 5       | 0                                  | 0                                 | 26                     | 0.42                                     | 0.41                                     | No            |
| 6       | 0                                  | 0                                 | 30                     | 0.44                                     | 0.39                                     | No            |
| 7       | 0                                  | 3                                 | 70                     | -                                        | -                                        | No            |
| 8       | 0                                  | 11                                | 47                     | -                                        | -                                        | No            |
| 9       | 0                                  | 0                                 | 52                     | -                                        | -                                        | No            |
| 10      | 3                                  | 1                                 | 14                     | -                                        | -                                        | No            |
| 11      | 0                                  | 3                                 | 32                     | 0.50                                     | 0.49                                     | Yes           |
| MEAN:   | 0.54 ± 1.2                         | 3.2 ± 3.6                         | 53 ± 14(k)             | 0.44 ± 0.06                              | 0.42 ± 0.06                              |               |
|         |                                    |                                   | 33 ± 22(λ)             |                                          |                                          |               |

Legend: HRF: hemodiafiltration with ultrafiltrate regeneration; QT: chemotherapy; FLC: free light chain; A: alive; D: dead.

Serum albumin concentration pre and post session were similar (0.44 ± 0.06 mmol/L pre vs. 0.42 ± 0.06 mmol/L post). The FLC removal from the UF by the cartridge at the beginning of the procedure was 99.2% for kappa and 97.06% for lambda light chains; the uptake of albumin was trivial (0.7%). At the end the session the capacity of the cartridge to adsorb kappa light chain was still very significant (63.7%); and the ability to remove lambda light was still sizeable (33.6%). The loss of albumin remained very low at the end of the procedure (0.015%). Moreover, no complications associated with the technique were observed.

In 4 patients (36.4%) (patients 2, 3, 4 and 11) the renal function improved after 2.2 ± 1.1 months of treatment and the mean creatinine decreased from 0.79 ± 0.39 mmol/L to 0.27 ± 0.11 mmol/L; then,
it continued to decrease until the end of the follow up (Creatinine: 0.18 ± 0.04 mmol/L). Two patients (18.2%) died during the first year (patients 1 and 5) and 5 patients (45.45%) required maintenance dialysis (patients 6,7,8,9 and 10). Patients 10 and 11 did not complete one year of follow-up. With respect to causes of deaths, patient 1, dependent on dialysis, died of septic shock ten days after an autotransplant of hematopoietic cells (7.5 months after diagnosis of MM). Patient 5, who was also dependent on dialysis, died of septic shock at month 11. Patient 4 recovered renal function but died 7 months later due to a septicemia (his creatinine was 0.22 mmol/L); and patient 6, who was dependent on dialysis, committed suicide at month 16.

Discussion

The present study was performed in patients with AKI secondary to MM to evaluate the effectiveness of hemodiafiltration with ultrafiltrate regeneration in reducing FLC and to determine whether there is albumin loss with this procedure. Our results show that the hemodiafiltration with ultrafiltrate regeneration technique produces an effective and sustained removal of FLC, without a significant loss of albumin. Therefore, this technique is effective as an adjunctive treatment for MM in combination with chemotherapy allowing the renal recovery in 36.4% of patients.

To our knowledge, the present report is the largest series of multiple myeloma patients treated with hemodiafiltration with ultrafiltrate regeneration. There were eleven patients analyzed, which may be sufficient to estimate the percentage reduction of FLC. The removal of FLC reported in other recent studies is around 84% for kappa [24] and 32.2–49.5% [25] or 69.3% [24] for lambda chains. Although other groups have shown a reduction of serum FLC with hemodiafiltration with ultrafiltrate regeneration [24–26], our study is the first that analyzes the concentration of FLC and albumin in both, blood and ultrafiltrate. The FLC reduction ratio obtained in the ultrafiltrate was greater than in blood. It was demonstrated that albumin was not adsorbed by the resin cartridge and was reinfused before the second chamber. Thus, the Super High Flux with polyphenylene membrane allowed the passage of FLC (especially kappa), without loss of albumin. According to the cut off of this first filter, which is the limiting factor for the FLC's blood extraction and on the basis of the dimeric composition of lambda chains, it can be assumed that in hemodiafiltration with ultrafiltrate regeneration the kappa chains extraction was twice as better than lambda. The polymethylmethacrylate (PMMA) membranes have obtained satisfactory results in terms of light chain removal [27], but the adsorption process is
limited by the saturation of the membrane. Standard PMMA hemodialysis (PMMA membrane BK 2.1 m² Toray®) was compared with an enhanced adsorption dialysis, which involves PMMA dialyzer replacement after 2 h. The reduction of FLC was greater in enhanced adsorption than standard PMMA dialysis: 31% for kappa and 53% for lambda vs. 22% for kappa and 21% for lambda. Thus, to maintain FLC reduction and avoid membrane saturation, it is required to replace the dialyzer during the session [28].

Other advantages of the hemodiafiltration with ultrafiltrate regeneration are: First, there was no decrease of albumin in blood and there was no adsorption of albumin to the resin; thus, albumin replacement is not required. That is a relevant advantage of this technique because combine hemodialysis with apheresis in a unique session of reasonable length, without the need for albumin replacement and the potential loss of other proteins of the immune system with a danger of infectious complications in subjects at a high risk due to the background haematologic disease. Second, in addition to avoiding further deposition of FLC to reduce the renal toxicity burden, it allows a rapid clearance of FLC that can be harmful elsewhere outside of the kidney, particularly amyloidogenic lambda chains for the heart. Third, there were no complications associated with the technique. Chevalier et al. have reported that the isonatric hemodiafiltration with ultrafiltrate regeneration even improve blood pressure control without augmenting intolerance symptoms [29]. It should be noticed that only 18.2% of the patients died at the first year and death was due to septic shock secondary to comorbidity associated with MM; another two patients also died during the follow-up, so total mortality during the entire follow-up was 36% (patients 1, 4, 5 and 6). Others have reported an increased mortality during the first year in MM patients undergoing hemodialysis treatment [30]. Yadav et al. shown that the median time to death in these patients was 5.1 months [31]. It is important to highlight that an early initiation of hemodialysis and prompt hemodialysis may improve the outcome [30].

In our study, renal recovery was achieved in three patients with kappa MM and in one patient with lambda MM. In a single-center study, renal recovery was associated with effective treatment of MM and a sustained reduction in the concentration of the involved FLC clone. The majority of patients who
recover renal function have no further need for dialysis [31]. It has been described that the median overall survival in people who recovered renal function was 62.4 [32] - 64.1 [31] months. Joseph et al. recently published that renal recovery is inversely associated with more aggressive malignancies, with a worse proteinuria and with a history of high-dose therapy combined with autologous stem cell transplantation [3]. The published data on renal recovery using PMMA is not uniform. Sens et al. showed that an intensive hemodialysis with PMMA (6 h session requiring two BK-F 2.1 m² dialyzers) was associated with high rates of renal recovery (71%) and survival (62% of patients were alive at 24 months) [33]. However, Hudier et al. did not observed a clear benefit on renal function after intensive hemodialysis with PMMA as compared with standard PMMA hemodialysis. Renal recovery rate was 38% after intensive hemodialysis and 35% in patients receiving standard hemodialysis [34]. Therefore, hemodiafiltration with ultrafiltrate regeneration achieves a greater and maintained reduction of FLC and has promising results on renal recovery as compared to other adsorptive techniques (PMMA).

Conclusions
In conclusion, hemodiafiltration with ultrafiltrate regeneration is a safe technique and provides a significant and sustained reduction of FLC in patients with AKI secondary to MM. The adsorptive capacity is maintained throughout the session and there is no loss of albumin. If hemodiafiltration with ultrafiltrate regeneration is used early in combination with effective chemotherapy, renal recovery is possible, regardless of the predominant type of light chains.

List Of Abbreviations
AKI: Acute Kidney Injury
FLC: Free light chains
HCO: High-Cut-Off
HFR-SUPRA: Hemodiafiltration with ultrafiltrate regeneration
MM: Multiple myeloma
PMMA: Polymethylmethacrylate
RRs: Reduction ratio per session
Declarations

**Ethics approval and consent to participate**

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Subjects have given their written informed consent prior to their inclusion in the study and the study protocol was approved by the institute’s committee on human research (committee’s reference number: 4334).

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

MAA reports grants, personal fees and non-financial support from Celgene, personal fees from Amgen, personal fees from Janssen, outside the submitted work; and AMM reports personal fees from Vifor pharma, personal fees from Medtronic, outside the submitted work. Rest of authors declare that they have no competing interests.

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**Author’s contributions**

MVPRM, RO, PA and AMM conceived and designed the work. MVPRM, MAAL, AN, CA, JCV and MAA performed substantial contributions to the acquisition and analysis of data for the work. MVPRM, RO,
PA, SS, MR and AMM interpreted the data for the work. All authors have participated in drafting the work or revising it critically, have done a final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figures
Figure 1

Diagram of hemodiafiltration with regeneration of the ultrafiltrate by adsorption in resin. 1: High permeability filter (Convection). 2: Resin cartridge (Adsorption). 3: Low permeability filter (Diffusion). Protocol of samples extraction: arterial blood pre (a) and post (b) dialysis (2 samples). Ultrafiltrate, pre (c) and post (d) resin, samples were taken at 5 minutes after starting the session (2 samples) and 5 minutes before the end of the session (2 samples). A total of six samples were collected during the procedure: 2 arterial blood samples and 4 samples of ultrafiltrate.