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Clinical Kidney Journal

ckj

OXFORD

Leading European Nephrology

Clinical Kidney Journal, 2018, vol. 11, no. 2, 230–235

doi: 10.1093/ckj/sfx079
Advance Access Publication Date: 22 August 2017
Original Article

ORIGINAL ARTICLE

Intensive haemodialysis using PMMA dialyser does not increase renal response rate in multiple myeloma patients with acute kidney injury

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Abstract

Background: Intensive haemodialysis (IHD) in addition to bortezomib-based chemotherapy might be efficient to rapidly decrease serum immunoglobulin-free light chains removal in patients with multiple myeloma (MM) and to improve renal prognosis and survival.

Methods: The aim of this retrospective multi-centre study was to compare the efficacy (renal recovery rate) of IHD and of standard haemodialysis (SHD) in patients with MM and dialysis-dependent acute kidney injury (AKI), concomitantly treated with bortezomib-based chemotherapy.

Results: We selected 41 patients with MM and dialysis-dependent AKI, most likely due to myeloma cast nephropathy (MCN), and who were treated in eight French hospitals between January 2007 and June 2011. Patients were classified in two groups according to dialysis regimen: IHD [$n = 21$, with a mean of 11.3 dialysis sessions all with poly(methyl methacrylate) (PMMA) membranes for 13.2 days] and SHD ($n = 20$ patients, mostly three times per week, 31% with PMMA membrane). The main outcome was dialysis-independence at 3 months. At 3 months, 15 patients could stop dialysis: 8 (38.1%) in the IHD and

Received: March 22, 2017. **Editorial decision:** June 19, 2017

7 (35%) in the SHD group (P = 1). Moreover, 14 (56%) of the 25 patients who did show haematological response and only one of the 16 patients who did not were dialysis-independent (P = 0.002) at 3 months.

Conclusions: The results of this retrospective study did not show any clear renal benefit of IHD in patients with MM and MCN compared with SHD. Conversely, they underline the importance of the haematological response to chemotherapy for the renal response and patient prognosis.

Key words: haematological response, intensive haemodialysis, multiple myeloma, PMMA, renal response

Introduction

Nowadays, the treatment of myeloma cast nephropathy (MCN) relies on chemotherapy, mainly using bortezomib and dexamethasone [1, 2]. In MCN, a hallmark of multiple myeloma (MM), serum immunoglobulin-free light chains (sFLC) produced by monoclonal plasma cells precipitate in renal tubules, resulting in tubular obstruction, local interstitial inflammation and ultimately kidney injury [3, 4]. Emerging data suggest the importance of extracorporeal removal of monoclonal sFLC [5–9]. Indeed, in patients with MCN, the reduced glomerular filtration rate (GFR) delays sFLC clearance and this might worsen renal damage [2–4, 10]. However, plasma exchange failed to show any clinical benefit in a large controlled and randomized clinical trial [11]. Nevertheless, Leung *et al.* have highlighted the positive relationship between sFLC reduction by half or more, following plasma exchange, and renal recovery rate in patients with biopsy-proven MCN [5]. Uncontrolled pilot studies [12–14] using high cut-off (HCO) membranes for daily haemodialysis showed up to 77% of dialysis-independence at 3 months in patients receiving chemotherapy (high-dose dexamethasone and novel anti-MM agents, including bortezomib) [7, 9]. In all these studies, renal recovery was linked to early and sustained sFLC plasma reduction. Recently, Burnette *et al.* reported that in 14 patients with biopsy-proven or highly probable MCN, among whom some were dialysis-dependent, plasma exchange and bortezomib-based therapy resulted in 86% of partial or complete renal response [15]. This suggests that reduction of FLC production (chemotherapy) and increase of FLC removal (plasma exchange) are both required to rapidly reduce sFLC renal precipitation and improve renal prognosis [15].

Ongoing controlled and randomized trials are assessing the efficacy and safety of intensive haemodialysis (IHD) strategies with HCO membranes combined with bortezomib-based chemotherapy [2, 16–18]. Moreover, data from *in vitro* studies suggest that poly(methyl methacrylate) (PMMA) membranes (BKF 2,1 Toray®) could also efficiently remove sFLC [12, 19]. Before the availability of HCO membranes and the beginning of the French Phase 3 multi-centre, controlled national clinical MYRE trial (NCT01208818), some French nephrologists already used PMMA membranes in daily haemodialysis schedules combined with bortezomib-based chemotherapy for MCN treatment [20, 21].

Therefore, the aim of our study was to retrospectively compare the efficacy (renal recovery rate) of IHD regimens with PMMA membranes and of standard haemodialysis (SHD) (both concomitantly with bortezomib-based chemotherapy) in patients with MM and dialysis-dependent acute kidney injury (AKI) consistent with MCN.

Materials and methods

For this multi-centre retrospective cohort study patients were recruited from eight different hospitals in western France from January 2007 to June 2011. In each centre, a list of all consecutive dialysis-dependent myeloma patients was established with the help of the referring nephrologists and the informatic department of medical information (PMSI) of each hospital to be exhaustive on dialysis myeloma patients. The relevant clinical information was collected in a database. This study was approved by the ethics committee of Rennes University Hospital (authorization #12–24).

Study population

Patients presenting AKI related to MM and requiring haemodialysis were included. MM was diagnosed according to the International Myeloma Working Group (IMWG) guidelines [22]. All patients were treated with bortezomib-based chemotherapy regimens, usually associated with dexamethasone.

All patients had AKI (without any previous kidney failure or in the framework of chronic kidney disease) that was considered to be linked to MCN because proteinuria included predominantly monoclonal immunoglobulin light chains (and absence of significant albuminuria) with plasma sFLC > 500 mg/L (Freelite®, Binding Site) [4]. However, renal biopsy was not mandatory for inclusion. Patients with transient renal failure that rapidly resolved after correction of hypercalcaemia and hydration were not included.

Patients must be treated with a chemotherapy regimen based on bortezomib, usually associated with dexamethasone.

Exclusion criteria were maintenance dialysis before the diagnosis of MM, or dialysis-dependent renal failure related to a cause other than supposed cast nephropathy, particularly amyloidosis in the case of important albuminuria.

Dialysis schedules

Patients were divided in two groups, depending on the dialysis schedule at treatment initiation. In the IHD group, patients underwent daily haemodialysis with PMMA membranes (PMMA Toray® 2.1 m^2 for 19 and 1.6 m^2 for 2 patients). In the SHD group, the haemodialysis regimen (mostly three times per week and always less than four times per week and using various membranes, including PMMA) was adapted to each patient's needs and in accordance with local habits. Type of membrane is shown in Supplementary data, Figure S1. The decision to start dialysis was taken by the treating physician, according to the local guidelines. As this is a retrospective study, blood and dialysate rate were not standardized, and dose of dialysis cannot be registered for all patients.

Outcomes—judgment criteria

The main evaluation criterion was dialysis-independence at 3 months.

Secondary outcomes were:

- Renal function after dialysis-independence, using the GFR estimated with the simplified Modification of Diet in Renal Disease (MDRD) equation [23, 24].
- Renal response classified according to the IMWG criteria [1].
- Haematological response defined as a 50% reduction of M protein level (complete immunoglobulin or sFLC) according to the IMWG criteria [22, 25]. All cases were reviewed by a referent myeloma specialist (O.D.) at Rennes University Hospital.
- sFLC reduction rate at 3 months.
- Death rate at 3 months.

Statistical analysis

For descriptive purposes, categorical variables were presented as numbers and proportions; continuous variables were assessed for normality (graphical method) and were reported as medians with interquartile range (IQR) or means ± standard deviation, as appropriate. Continuous variables were compared using the Wilcoxon test. Categorical variables were compared using the χ^2 or Fisher's exact test. All statistical analyses were carried out using the SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Study population

All dialysis requiring myeloma patients hospitalized in the eight hospitals from January 2007 to June 2011, corresponding to 41 patients, were included. The patients' characteristics are summarized in Table 1. Patients in the SHD group were significantly older and had higher blood creatinine levels at dialysis initiation. Conversely, MM characteristics and AKI complications were comparable between groups. All patients received bortezomib and dexamethasone as chemotherapy, with the exception of one patient who was treated only with bortezomib because of psychiatric intolerance to corticosteroids. Four patients received also melphalan and one thalidomide. The median number of chemotherapy cycles was five (IQR = 3.5) in both groups (P = 0.28).

In the IHD group ($n = 21$), patients underwent intensive dialysis with PMMA membranes with a mean of 11.3 ± 4 (range: 6–21) dialysis sessions in 13.2 ± 4 days (range: 7–22) after dialysis initiation. The mean dialysis session duration was 4.5 ± 0.8 h (range: 3–6 h). In the SHD group ($n = 20$), patients underwent haemodialysis according to their needs and local guidelines, mostly three times per week and always less than four times, 31% of patients in the SHD group were treated with PMMA membranes. Kidney biopsy was performed in 13 patients (31% of the total sample; 9 IHD and 4 SHD patients) and histology analysis confirmed the presence of MCN, associated with some degree of interstitial fibrosis/tubular atrophy. Neither immunoglobulin deposition nor amyloidosis was detected in these biopsies.

Renal response is comparable after IHD or SHD

At 3 months, eight patients in the IHD group (38.1%) and seven in the SHD group (35%) were dialysis-independent (P = 1). The median time to dialysis independence was 0.6 months in the IHD and 1.3 months in the SHD group (P = 0.4). The median GFR

Table 1. Population baseline characteristics

	Total population $n = 41$	IHD $n = 21$	SHD $n = 20$	P (between IHD and SHD)
General characteristics				
Age (years)[a]	72 (17)	68 (19)	77 (10)	0.02
Age <65 years[b]	13 (31.7%)	9 (42.8%)	4 (20%)	0.16
Age >75 years[b]	15 (36.6%)	4 (19%)	11 (55%)	0.02
Men[b]	20 (48.8%)	9 (42.8%)	11 (55%)	0.54
Renal parameters				
Creatinine at dialysis initiation (μmol/L)[a]	598 (356)	477 (375)	723 (822)	0.05
AKI on chronic renal disease[b]	6 (14.6%)	2/19 (10.5%)	4/19 (21%)	0.66
Renal biopsy[b]	13 (31.7%)	9 (42.8%)	4 (20%)	0.18
Proteinuria (g/24 h)[a]	2.98 (2.6)	2.7 (1.5)	3.7 (3)	0.10
Proteinuria ≥2 g/24 h[b]	30/38 (78.9%)	16/21 (76.1%)	14/17 (82.3%)	0.70
MM characteristics				
sFLC (mg/L)[a]	6870 (10740)	5475 (10396)	9680 (16276)	0.19
M protein by ELP (g/L)[a]	19.3 (37.8)	36 (41)	17 (14)	0.26
Monoclonal plasma cells in bone marrow[a]	27.5% (37)	30%	25%	0.87
MM IgG[b]	18 (43.9%)	8 (38%)	10 (50%)	0.54
MM LC[b]	17 (41.5%)	8 (38.1%)	9 (45%)	0.76
De novo MM[b]	29 (70.7%)	15 (71.4%)	14 (70%)	1.00
Kappa sFLCs[b]	20 (48.8%)	9 (42.8%)	11 (55%)	0.54
Plasma cell leukaemia[b]	3 (7.3%)	0	3 (15%)	0.10
Main complications				
Anaemia (haemoglobin level, g/dL)[a]	8.75 (2.15)	8.45 (2.6)	9.1 (2)	0.18
Lytic bone lesions[b]	30/40 (75%)	15/20 (75%)	15 (75%)	1.00
Hypercalcaemia (> 3 mmol/L)[b]	5/40 (12.5%)	3/20 (15%)	2 (10%)	1.00
Identified AKI precipitating factor[b]	26 (63.4%)	13 (61.9%)	13 (65%)	1.00

[a]Median and IQR.
[b]Number and (percentage).
ELP, electrophoresis; LC, light chains.

value after dialysis-independence was 34 mL/min/1.73 m^2 for the IHD and 27 mL/min/1.73 m^2 for the SHD patients (P = 0.4). Three IHD patients and one SHD patient reported complete renal response. One IHD and three SHD patients were dead and all still on dialysis at the time of death (P = 0.34).

After 1 year, 12 patients in the IHD group (57%) and 6 in the SHD group (30%) were dialysis-independent (P = 0.12) and 4 (IHD group) and 7 (SHD group) were dead (P = 0.31).

The renal response is associated with the haematological response in both IHD and SHD groups

Overall, 25 patients (61% of 41) had achieved haematological response at 3 months. Moreover, 14 (56%) of them were also dialysis-independent, whereas only one of the 16 haematological non-responders was dialysis-independent at 3 months (P = 0.002). Among the 25 haematological responders, 15 were in the IHD group (71.4% of 21) and 10 in the SHD group (50% of 20) (P = 0.21 between groups). Dialysis-independence was achieved by 8 of the 15 (53.3%) haematological responders in the IHD group and 6 of the 10 (60%) responders in the SHD group (P = 1). In conclusion, among the 15 patients who became dialysis-independent at 3 months, only one did not show haematological response. Conversely, 11 of the 22 (50%) patients who continued maintenance haemodialysis showed haematological response at 3 months (P = 0.02). The only patient who became dialysis-independent without achieving haematological response belonged to the SHD group.

sFLC concentration was available at baseline (Day 1 of dialysis) and at 3 months for 16 (76.2%) IHD patients and 11 (55%) SHD patients. At 3 months, an sFLC decrease of 50% or more was observed in 12/16 IHD patients (75%) and in 9/11 SHD patients (81.8%) (P = 1). Among these patients, seven IHD patients (58.3%) and five SHD patients (55.5%) were also dialysis-independent at 3 months (P = 1). All patients who did not show a 50% sFLC reduction after 3 months (four in the IHD and two in the SHD) were all on maintenance haemodialysis at the end of the study.

Table 2 summarizes the characteristics of the patients subdivided according to their renal response (dialysis independence or not). The only two factors that significantly associated with the renal response were the haematological response and a reduction of the sFLC of at least 50%. Due to the limited number of patients, multivariate analyses could not be performed.

Discussion

We retrospectively studied a cohort of 41 patients with MM and dialysis-dependent AKI treated with IHD or SHD. Our results indicate that renal recovery rate is not better with intensive dialysis and that the renal response rate is highly correlated with the haematological response.

Our finding that haematological response was observed in 14 of the 15 patients who became dialysis-independent confirms that the haematological response is the most important determinant of renal recovery. Hutchison *et al*. reported high renal recovery rate using an extended HCO-based haemodialysis regimen combined with chemotherapy [13]. However, in this uncontrolled study, sustained FLC reduction was only observed in patients who did not interrupt chemotherapy. Indeed, five of the six patients who had to stop chemotherapy (mostly due to infections) remained dialysis-dependent in our cohort. In our study, the haematological response rate was around 60% with bortezomib-based therapy, a relatively low percentage and close to that of other studies in non-dialysed patients.

Table 2. Population characteristics according to the renal response

	At 3 months		
	Patients with renal response $n = 15$	Patients without renal response $n = 26$	P
Age (years)[a]	75 (10)	70 (23)	0.11
Age <65 years[b]	2 (13.3%)	11 (42.3%)	0.17
Age >75 years[b]	7 (46.6%)	8 (30.8%)	0.34
Men[b]	5 (33.3%)	15 (57.7%)	0.2
Creatinine at dialysis initiation (μmol/L) [a]	517 (372)	632 (351)	0.32
Intensive dialysis (yes/no)	8/7	13/13	0.837
Proteinuria (g/24 h) [a]	3 (2.6)	3 (3)	0.23
Proteinuria >2 g/24 h[b]	9/13 (69.2%)	21/25 (84%)	0.4
Renal biopsy[b]	3 (20%)	10 (38.5%)	0.3
AKI on chronic renal failure[b]	3 (20%)	3 (11.5%)	0.65
Peak sFLC (mg/L)[a]	9680 (1087)	5684 (9870)	0.71
Peak M protein (g/L) [a]	28 (20)	16 (38)	0.57
MM LC[b]	7 (46.6%)	10 (38.5%)	0.75
de novo MM[b]	10 (66.6%)	19 (73%)	0.73
Kappa sFLC subtype[b]	5 (33.3%)	15 (57.7%)	0.2
Plasma cell leukaemia[b]	0	3 (11.5%)	0.29
Anaemia (haemoglobin, g/dL) [a]	8 (2)	9 (2)	0.65
Bone lesions[b]	10 (66.6%)	20/25 (80%)	0.46
Hypercalcaemia (>3mmol/L) [b]	1/14 (7.1%)	4 (15.4%)	0.64
Identified AKI precipitating factor[b]	7 (46.6%)	19 (73%)	0.11
Chemotherapy cycles[a]	6 (3)	5 (4)	0.61
50% or more sFLC reduction[b]	12/12 (100%)	9/15 (60%)	0.02
Haematological response[b]	14 (93.3%)	11 (42.3%)	0.002

[a]Median and IQR.
[b]Number and (percentage).
LC, light chains.

To our knowledge, this is the largest published cohort study about extra-corporeal sFLC removal using IHD and PMMA membranes ($n = 21$ patients) and with a control group (20 patients who underwent SHD). Importantly, all patients were treated with the same bortezomib-based chemotherapy regimen and were dialysis-dependent. Previous studies on extracorporeal FLC removal were uncontrolled [6, 7, 9, 13, 26], whereas controlled studies on MM treatment often did not include dialysis-dependent patients. Only the median age and the initial creatinine level, which are adverse prognostic factors, were significantly higher in the SHD than in the IHD group. These differences (older age, higher serum creatininaemia despite a possible lower muscle mass) could have biased our results, leading to better results in the less advanced disease group of patients. However, even with these differences, IHD was not associated with higher renal recovery rates.

The rational of using IHD regimens comes from studies showing a link between the renal recovery and the reduction of sFLC concentration [5–7]. Indeed, none of our patients with a reduction of sFLC concentration lower than 50% showed renal function recovery. sFLC concentration depends on FLC production rate, distribution volume and elimination [12]. Thus, low sFLC level can be the result of both reduced production (chemotherapy) and optimal elimination (haemodialysis). Hutchison *et al.* showed, using an *in vitro* model of FLC production, distribution and metabolism in patients with MM [12], that active tumour treatment is required for maintaining low sFLC levels and that sFLC concentration in the first days or weeks is negatively correlated with the renal recovery rate [6, 7]. Some of the studies in favour of extra-corporeal sFLC removal incorporated different chemotherapy regimens, precluding definitive conclusions [6, 7, 9, 13, 26]. Conversely, in our study, all patients received bortezomib-based therapy and only the haemodialysis regimen was different between groups. Moreover, our results are consistent with those by Burnette *et al.*, showing that in 14 patients with MCN treated with bortezomib-based therapy and plasma exchange, removal and reduction of light chain production are both required for efficiently improving renal function [15]. Differently from our present work, this study did not include only dialysis-dependent patients.

Our study has some limitations. First, although IHD did not bring more benefits compared with SHD, the haemodialysis schedules in the IHD group could be further optimized to maximize sFLC removal. Specifically, sFLC removal by PMMA membranes occurs mostly because of adsorption [12] and these membranes are saturated after 3 h [12, 27, 28]. Therefore, haemodialysis sessions longer than 3 h with the same membrane do not further increase sFLC removal. Moreover, the very high circulating levels of sFLC in patients with dialysis-dependent MCN could have led to faster membrane saturation. Changing the membrane in the middle of a 6-h session could have changed our results and this hypothesis should be evaluated. Another option is to use HCO membranes, which are protein-leaking membranes [16]. Intensive dialysis with HCO membranes will then remove more rapidly even high levels of sFLC and not be saturable. In consequence, according to first results of ongoing studies, intensive dialysis with HCO membranes seems to be more effective for MCN [16, 18, 29].

Secondly, this was a retrospective study, although with a control group. Moreover, as dialysis-dependent patients with MM are rare, the number of patients was limited, but similar in both groups, and statistical tools suitable for small samples were used. However, we cannot exclude that the absence of significant difference between dialysis modalities could in part be due to low statistical power. Ongoing larger, randomized clinical trials in which bortezomib-based chemotherapy and extracorporal light chain removal are used, like in our study, will formally answer the question [2, 16, 18, 29].

Thirdly, while Hutchinson *et al.* showed that FLC reduction needs to occur within the first 3 weeks of AKI [6–8], we could not compare early sFLC removal between groups because of the retrospective study design. Nevertheless, comparison of sFLC levels at baseline and at 3 months (data available only for 55% of patients) showed that sFLC reduction at 3 months is also a good prognostic factor.

Finally, a limited number of patients (31%) underwent kidney biopsy. This percentage is similar to what was reported in other recent studies [9, 26]. Like in the retrospective study by Burnette *et al.* who did not specify how many patients had a kidney biopsy [15], we excluded patients with transient renal failure and confounding factors. Moreover, the timing of renal recovery suggests that no patient with functional acute renal failure was included. We also excluded patients with nephropathy and important albuminuria in order to eliminate amyloidosis as the cause of AKI. However, only biopsy can confirm the absence of another underlying nephropathy (such as chronic vascular nephropathy, severe interstitial fibrosis/tubular atrophy, immunoglobulin deposition disease, etc.) that could explain the end-stage renal disease. Similarly, only a biopsy can confirm that the rapid renal recovery is due to MCN regression and not to functional acute renal failure reversal or elimination of AKI precipitating factors.

Conclusion

We retrospectively compared 21 patients who received IHD and 20 patients who received SHD for dialysis-dependent AKI concomitantly with bortezomib-based chemotherapy. Renal response was not significantly different between haemodialysis schedules. Conversely, the haematological response was associated with the renal response. The main limitations of our study are the retrospective design, small number of patients, non-optimal use of PMMA membranes (no change after 3 h) and lack of histological confirmation of the diagnosis of MCN for all patients. Considering the cost (human and material) of these intensive regimens with HCO membrane, realization of large prospective trials is crucial. Only those large ongoing randomized trials will be able to answer the question of whether extracorporeal sFLC removal using HCO membrane can help renal recovery in patients with MM; however, our results already emphasize the importance of bortezomib-based chemotherapy for patients with MM and suspected MCN.

Supplementary data

Supplementary data are available online at http://ckj.oxfordjournals.org.

Acknowledgements

We thank Elisabetta Andermacher for attentive English revision.

Funding

O. Decaux has speaker and travel honorarias.

Conflict of interest statement

O.D. received honoraria from Janssen-Cilag. The remaining authors declare no competing financial interests.

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