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Improvement of cast nephropathy with plasma exchange depends on the diagnosis and on reduction of serum free light chains

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Cast nephropathy is the most common cause of renal disease in multiple myeloma, however, treatment with plasma exchange remains controversial even after 3 randomized controlled studies. We sought to determine the importance of diagnostic confirmation and goal directed therapy in the treatment of cast nephropathy in forty patients with confirmed multiple myeloma and renal failure who underwent plasma exchange. A positive renal response was defined as a decrease by half in the presenting serum creatinine and dialysis independence. No baseline differences were noted between eventual renal responders and non-responders. Three quarters of the patients with biopsy proven cast nephropathy resolved their renal disease when the free light chains present in the serum were reduced by half or more but there was no significant response when the reduction was less. The median time to a response was about 2 months. In patients without cast nephropathy, renal recovery occurred despite reductions in free light chain levels of the serum. No association was found between free light chains in the serum, urinary monoclonal proteins, overall proteinuria and cast nephropathy. We found that the relationship between renal recovery and free light chain reduction was present only in patients with biopsy proven cast nephropathy showing the importance of extracorporeal light chain removal in this disease.

Kidney International (2008) **73,** 1282–1288; doi:10.1038/ki.2008.108; published online 2 April 2008

KEYWORDS: plasma exchange; cast nephropathy; myeloma kidney

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Received 11 October 2007; revised 14 January 2008; accepted 22 January 2008; published online 2 April 2008

Renal failure is a common and serious sequela of multiple myeloma. Reported incidence ranges from 18 to 56% depending on definition.[1–4] If not reversed, renal failure can extol a significant impact on survival.[2,5,6] Although presentation may be similar, the etiology is heterogenous. The most common cause is light chain cast nephropathy (CN) seen in ~30% of the patients.[7,8] Other more common etiologies include immunoglobulin light-chain amyloidosis (AL) and monoclonal immunoglobulin deposition disease. AL and the rarer heavy-chain amyloidosis account for 5–11% of the cases, whereas monoclonal immunoglobulin deposition disease occurs at roughly half that frequency.[8,9] Subtypes of monoclonal immunoglobulin deposition disease include light-chain deposition disease (LCDD), light heavy-chain deposition disease, and heavy-chain deposition disease.[10,11] Acute tubular necrosis (ATN) is common since nephrotoxicity from non-steroidal anti-inflammatory drugs and iodinated contrast is enhanced in myeloma patients.[9] Less frequent renal manifestations include cryoglobulinemia, proliferative glomerulonephritis, crystalline nephropathy, and so on.[12–17] More than one histological pattern can exist in the same kidney. The most common combinations are CN with ATN and CN with monoclonal immunoglobulin deposition disease.[8,9,18]

The treatment of CN is controversial. To date, three randomized controlled trials have evaluated the effectiveness of plasma exchange (PLEX). Zucchelli *et al.*[19] randomized 29 patients with serum creatinine (Scr) >5 mg per 100 ml to receive hemodialysis and PLEX vs peritoneal dialysis. Eleven patients from each group required dialysis. Renal function improved in 13/15 treated with PLEX vs only 2/14 with peritoneal dialysis. Unfortunately, five patients in the latter group died within the first 2 months, and this was often cited as a major weakness of the study. Johnson *et al.*[20] reported on 21 patients, 12 of whom were on dialysis. Eleven patients were randomized to receive PLEX. They noted no differences in the overall renal recovery rate (control 50% vs PLEX 64%, $P = NS$); however, in a subgroup analysis of the dialysis patients, renal recovery occurred only in those who received

PLEX. The third and largest study published by Clark *et al.*[21] involved 97 patients. Fourteen of the 39 control patients and 15/58 PLEX patients were on dialysis at baseline. In this study, 69% of the control group and 58% of the PLEX group reached a composite outcome, which included death, dialysis dependence, or an estimated glomerular filtration rate (eGFR) $<30\,ml\,min^{-1}\,1.73\,m^{-2}$ at 6 months. The difference was not statistically significant ($P=0.36$) and PLEX was felt to be ineffective.

Although Clark's study was the largest of the three trials, it also had the most serious limitations. First, despite being the largest, the number of patients in Clark's study was still small and was at risk for beta error. This was further compromised by the use of a composite outcome which disadvantaged PLEX because patient who died with improved renal function and those with eGFR $<30\,ml\,min^{-1}\,1.73\,m^{-2}$ were considered failures. The most serious limitation however was that the renal pathology was not verified due to the low biopsy rate. Finally, no method was employed to assess the adequacy of treatment. Thus, the efficacy of PLEX in the treatment of cast nephropathy remains unsettled. Given the importance of renal recovery in these patients, we performed this retrospective study to investigate the effectiveness of PLEX in the treatment of CN, when the diagnosis is confirmed by renal biopsy and the treatment is guided by serum-free, light-chain levels.

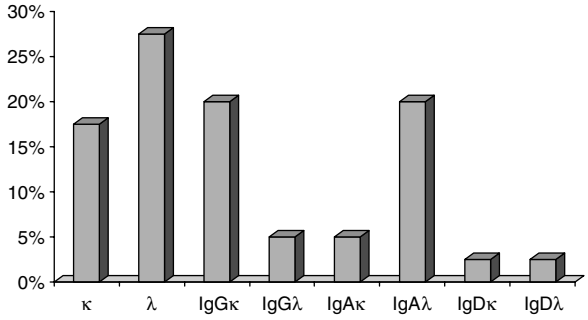

Figure 1 | The distribution of monoclonal proteins amongst patients with multiple myeloma and renal failure.

RESULTS

Forty patients met the inclusion criteria. Myeloma was newly diagnosed in 67.5%. Median age was 67 (range 35–84 years) with 60% male. Light chains were 45% κ, 55% λ. Eighteen patients had monoclonal light chains without an intact immunoglobulin (Figure 1). Baseline serum free light chain (sFLC) was only available for 77.5%, since the Freelite™ assay was not commercially available until late 2001, and was not used in our institution until late 2002–early 2003 (Figure 2a). On the other hand, baseline serum M-protein was measured in 97.5%. Serum FLC levels ranged from 3.3 to 8080 mg per 100 ml (normal values for $\kappa=0.33$–1.94 mg per 100 ml, $\lambda=0.57$–2.63 mg per 100 ml). The lowest sFLC level from a biopsy proven CN was 157 mg per 100 ml. The highest sFLC level belonged to a patient with pure LCDD. Median proteinuria was $3.1\,g\,day^{-1}$ (0.6–$17.5\,g\,day^{-1}$) and urine M-spike was $1.7\,g\,day^{-1}$ (0.01–$15.3\,g\,day^{-1}$).

Median presenting Scr was 4.8 mg per 100 ml (2.0–18.6 mg per 100 ml) corresponding to an eGFR of 11.0 (3–34) $ml\,min^{-1}1.73\,m\text{-}^{2}$. A historical Scr was available for 67.5%, but only 10 were within 45 days of presentation. Nine

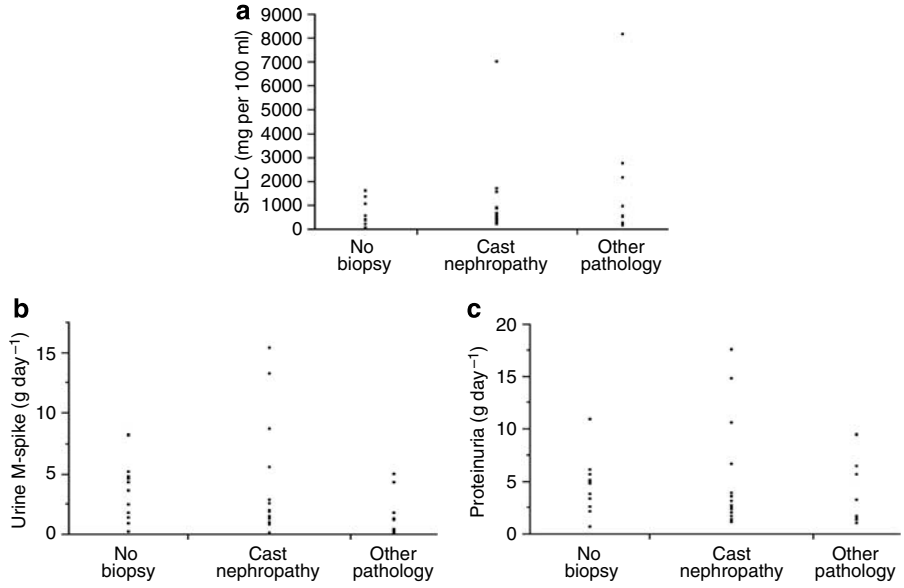

Figure 2 | Distribution of SFLC, urine M-spike and proteinuria in relation to renal pathology. (**a**) Serum FLC levels were similar amongst patients with no biopsy 369 mg per 100 ml (3–1560), cast nephropathy 467 mg per 100 ml (157–6960), and other renal pathology 711 mg per 100 ml (106–8080); $P=0.40$. (**b**) No significant difference was found in the urine M-spike for patients with no kidney biopsy $3.5\,g\,day^{-1}$ (0.1–8.1), cast nephropathy $1.7\,g\,day^{-1}$ (<0.1–15.3), and other pathology $1.1\,g\,day^{-1}$ (<0.1–4.9); $P=0.25$. (**c**) Median proteinuria for patients with no kidney biopsy was $4.6\,g\,day^{-1}$ (0.6–10.7), $2.6\,g\,day^{-1}$ (1.0–17.5) in cast nephropathy, and $2.3\,g\,day^{-1}$ (0.9–9.4) in other pathology. No significant difference was noted; $P=0.55$.

Table 1 | Renal pathology in renal responders and non-responders

Renal pathology	Non-responders	Renal responders
Cast nephropathy	6	7
CN+tubulointerstitial nephritis	1	2
CN+chronic interstitial nephritis	2	0
CN+LCDD	1	1
LCDD	3	0
AL amyloidosis	0	1
ATN	2	2

CN, cast nephropathy; AL, immunoglobulin light-chain associated amyloidosis; ATN, acute tubular necrosis; LCDD, light-chain deposition disease.
No patient with pure LCDD responded and only 2 of 4 patients with ATN responded after PLEX.

patients (22.5%) required dialysis at presentation. Another initiated dialysis while receiving PLEX and 3 others with Scr of 3.0, 5.9 and 8.8 mg per 100 ml became dialysis dependent much later. Two patients who presented with Scr of 18.8 and 4.3 mg per 100 ml became dialysis independent. Eleven patients were dialysis dependent at the time of the study. Eight patients had exposure to nephrotoxins: 5 non-steroidal anti-inflammatory drugs, 2 intravenous contrast and 1 zoledronic acid. Other comorbidities included hypercalcemia (2), plasma cell leukemia (2), large gastrointestinal bleeding (1), and fever (2).

Twenty-eight (70%) patients underwent renal biopsy without any serious complications. Pure CN was identified in 18 (64.3%), with five patients having tubulointerstitial infiltrates, of which two were chronic (Table 1). Neither initial sFLC level ($P=0.38$), serum M-protein ($P=0.89$), nor urine M-protein ($P=0.18$), were predictive of CN. Other renal pathologies included CN with LCDD (2), ATN (3), LCDD (3), diabetic nephropathy with ATN (1), and AL amyloidosis (1). Two other patients who did not have a renal biopsy had amyloid identified on fat aspirate (1) and bone marrow (1). In patients with CN, the median presenting Scr was 4.8 mg per 100 ml (2.0–18.6 mg per 100 ml), vs 5.5 mg per 100 ml (3.1–11.4 mg per 100 ml) in other renal pathology and 4.2 mg per 100 ml (2.1–9.3 mg per 100 ml) in those without a renal biopsy ($P=0.72$). Thirty-one patients had sFLC measured prior to PLEX. Median initial sFLC level of CN patients was 466.5 (157–6960 mg per 100 ml), vs 711 (106–8080 mg per 100 ml) in other renal pathology and 369 (3.3–1560 mg per 100 ml) in those with no renal biopsy, $P=0.40$. Urine protein and M-spike were measured in 85% of patients. No differences were noted in the urine M-spike or proteinuria among the three groups (Figure 2b and c).

Overall, 18 of 40 (45%) patients achieved a renal response after PLEX. No differences in age (68 vs 64 years, $P=0.1$) or sex (50% males vs 72.2% males, $P=0.15$) were noted between non-responders and responders respectively. The baseline Scr (4.8 vs 4.8 mg per 100 ml, $P=0.47$) and eGFR (11.0 vs 11.5 ml min^{-1}1.73 m^{-2}, $P=0.69$) were also similar between responders and non-responders respectively. Renal response was similar between patients with a historical Scr ($P=0.44$), renal biopsy ($P=0.68$), pre and posttreatment sFLC measurements ($P=0.71$), and those without. Median Scr of responders was 3.0 mg/dl (1.6–7.0 mg/dl) after PLEX and improved to 1.4 mg/dl (0.8–2.7 mg per 100 ml) at their best. This represented an eGFR of 44.5 (26–102) ml min^{-1}1.73 m^{-2}. The median time to renal response was 61 days (3–170). In contrast, the non-responders had a significantly higher posttreatment Scr (4.4 mg per 100 ml (2.2 mg per 100 ml to dialysis), $P<0.001$) and lower eGFR (12.5 ml min^{-1}1.73 m^{-2} (dialysis to 26 ml min^{-1}1.73 m^{-2}), $P<0.001$). Half of the non-responders became dialysis dependent. No patient with LCDD responded but 1 of 2 patients with CN and LCDD did. Two of the nine patients who presented on dialysis recovered their renal function. Renal response also occurred in 4 patients who did not have pure CN, (2) ATN, (1) AL amyloidosis, and (1) CN with LCDD.

Twenty-eight patients had sFLC measured before and after PLEX, 22 of whom also had a renal biopsy (Table 2). Renal response was noted in 14 patients (50%). Serum FLC was reduced by $>50\%$ in 11 of 14 renal responders, but in only 6 of 14 non-responders ($P=0.05$; Figure 3). Renal response occurred without 50% sFLC reduction in three patients (1 AL, 1 ATN, and 1 was not biopsied). Their posttreatment sFLC were between 215–1120 mg per 100 ml. On the other hand, 6 patients (3 LCDD, 1 diabetic nephropathy, 1 CN with an interstitial nephritis, and fibrosis and 1 CN precipitated by intravenous contrast and had been on dialysis for 1 month prior to diagnosis) had $>50\%$ sFLC reduction, but did not achieve renal response.

The effect of sFLC reduction on renal response was most important in the CN patients. In the 14 of 18 patients with CN who had sFLC measured before and after PLEX, renal response occurred in 77.8% (7/9) whose sFLC was reduced by 50% or more. One patient with chronic changes on the renal biopsy and one whose renal failure was precipitated by intravenous contrast did not respond. None of the five patients with $<50\%$ reduction in sFLC had a renal response. This difference in renal response between patients with $>50\%$ and $<50\%$ sFLC reduction was highly significant ($P=0.005$). Two patients whose sFLC reduction could not be assessed also had a renal response.

Renal response was dependent on posttreatment sFLC levels only in the patients with CN. The median posttreatment sFLC of all responders was 131 mg per 100 ml (72–1120 mg per 100 ml) vs 262 mg per 100 ml (30–4780 mg per 100 ml) in all non-responders, $P=0.10$. However, when CN patients were analyzed separately, posttreatment sFLC was significantly higher in the non-responders (272.5 mg per 100 ml (86–1020 mg per 100 ml) compared with responders 92.6 (79.2–143 mg per 100 ml), $P=0.03$). This difference between responders and non-responders was not seen in patients with other pathology (312 vs 50.6 mg per 100 ml respectively, $P=0.40$) or patients without a renal biopsy (218 vs 390.5 mg per 100 ml, respectively, $P=0.99$). In a logistic regression model that adjusted for age, sex, and CN, renal

Table 2 | Characteristics and responses of patients with renal biopsy

	Other pathology	Cast nephropathy	*P*-value
N	10	18	
Age	69 (56–78)	65.5 (35–81)	0.29
Male	80%	44.4%	0.06
Initial Scr (mg per 100 ml)	5.5 (3.1–11.4)	4.8 (2–18.6)	0.73
Best Scr	4.3 (0.8–dialysis)	2.3 (1.2–dialysis)	0.33
Initial eGFR (ml min^{-1} 1.73 m^{-2})	10 (5–21)	11.5 (3–34)	0.55
Best eGFR	15 (5–102)	24.5 (5–54)	0.80
Renal biopsy results			
Cast nephropathy	0%	100%	
ATN	30%		
CN+LCDD	20%		
LCDD	30%		
AL	10%		
Diabetic nephropathy	10%		
Chemotherapy			0.18
Dex/steroids alone	60%	50%	
Melphalan and steroids	10%	5.6%	
Thalidomide Dex	10%	16.7%	
Bortezomib and Dex	0%	5.6%	
VAD	0%	5.6%	
MPT	10%	0%	
Alemtuzumab	0%	5.6%	
Cyclophosphamide	0%	11.1%	
None	10%	0%	
Outcome			
Renal response	30%	50%	0.30
Dialysis at baseline	20%	27.8%	0.64
At 6 months	40%	22.2%	0.32
Mortality at 6 months	20%	22%	0.89
sFLC response to PLEX			
N	8	14	
sFLC (mg per 100 ml)			
Initial	711 (106–8080)	466.5 (157–6960)	0.40
After PLEX	211 (30–4780)	143 (79–1020)	0.16
50% sFLC reduction	75%	64.3%	0.60

AL, light-chain amyloidosis; ATN, acute tubular necrosis; CN, cast nephropathy; DEX, dexamethasone; eGFR, estimated glomerular filtration rate; LCDD, light-chain deposition disease; MPT, melphalan, prednisone, and thalidomide; Scr, serum creatinine; sFLC, serum free light chain; VAD, vincristine, adriamycin, and dexamethasone.
Best Scr and eGFR were obtained from the best Scr after PLEX treatment.
Data on free light chain response to plasma exchange were collected on 22 of 28 patients. The rest of the data reflect all 28 patients with a renal biopsy.

response was predicted by either posttreatment sFLC level ($P=0.02$) or $>50\%$ reduction of sFLC ($P=0.02$).

The average number of PLEX performed was 6 (1–19). This was higher for patients with CN than those with other renal pathology (7.5 (2–19) vs 5.5 (2–7), respectively, $P=0.01$). Patients without renal biopsy had 6.5 (1–12) exchanges similar to patients with CN ($P=0.64$). The number of PLEX did not differ significantly between renal responders and non-responders (5.5 (1–12) vs 6.5 (2–19) respectively, $P=0.28$). No relationship was found between the number of PLEX and the posttreatment sFLC levels ($P=0.9$).

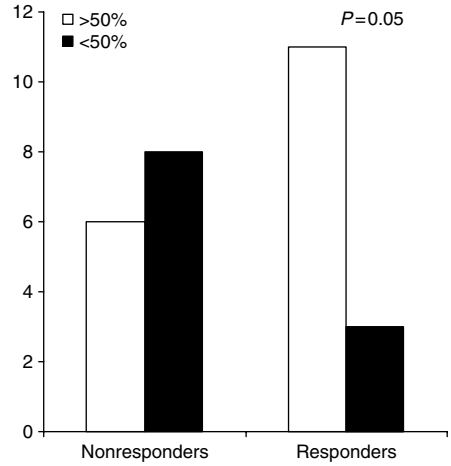

Figure 3 | Renal response by reduction of sFLCs. Of the six patients with $>50\%$ reduction in sFLC without renal response, 3 had LCDD, 1 had diabetic nephropathy with acute tubular necrosis, 1 had cast nephropathy precipitated by intravenous contrast, and 1 had cast nephropathy with atypical tubulointerstitial nephritis and fibrosis. Three patients had $<50\%$ reduction in sFLC and renal response. One had AL amyloidosis, 1 had ATN, and 1 was not biopsied.

Comorbidities appeared to have an impact on renal recovery. No patients with plasma-cell leukemia achieved renal response but both patients with hypercalcemia did. Unfortunately, the percentage of sFLC reduction could not be determined for these four patients. In five patients who took non-steroidal anti-inflammatory drugs, only the two with $>50\%$ sFLC reduction achieved renal response. Both patients with fever and one with gastrointestinal hemorrhage achieved renal response, but sFLC was reduced by $>50\%$ in only one of the fevers. None of the patients who developed renal failure as a result of intravenous contrast (2) or zoledronic acid (1) recovered their renal function despite $>50\%$ sFLC reduction in one of contrast patients. Comorbidity as a whole did not differ between renal responders and non-responders (38.9 vs 40.9%, $P=0.90$). However, patients who had either plasma-cell leukemia, contrast, or zoledronic acid were less likely to achieve renal response ($P=0.01$). Despite that, these factors were not found to be independent predictors of renal response in the multivariate analysis.

Chemotherapy was used during PLEX in 85% of the patients. The most common chemotherapeutic regimen was high-dose dexamethasone. Renal response rate was 45% in those treated with high-dose dexamethasone and PLEX. In those with $>50\%$ reduction in sFLC, renal response rate was 71.4 vs 20% for those who did not ($P=0.1$). The effect of different chemotherapy regimen on renal response could not be determined due to the small numbers. Survival was significantly longer in patients who achieved renal response. Median survival was 31.8 months for renal responders vs 11.0 months for non-responders (Figure 4). When survival was analyzed for the impact of newly diagnosed vs relapsed myeloma, significantly differences were noted ($P=0.0002$). This difference remained significant in a multivariate analysis

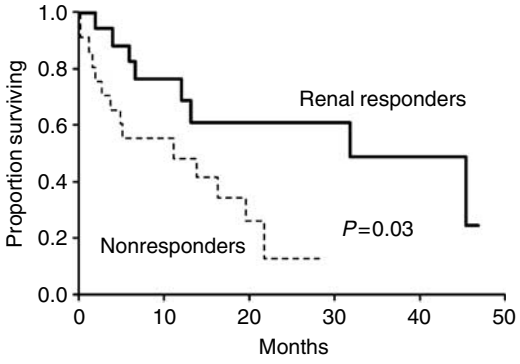

Figure 4 | Patient survival based on renal response. Median survival for renal responders was 31.8 months vs 11.0 months in non-responders; $P = 0.03$.

($P = 0.004$) and was found to be even more important than renal response ($P = 0.07$).

DISCUSSION

Plasma exchange was first used in the treatment of acute renal failure associated with multiple myeloma in 1976.[22] Since then, dozens of case reports and two randomized trials have documented its efficacy.[19,20] This led to a consensus statement by the Scientific Advisors of the International Myeloma Foundation formally endorsing its use.[23] Less than 3 years later, the results of a multicenter trial from Canada challenged the effectiveness of PLEX and the consensus statement.[21] As a result, the American Society for Apheresis downgraded the use of PLEX in renal failure associated with multiple myeloma from a Category II indication (accepted as a supportive or adjunct therapy) to a Category III indication (suggestion of benefit for which existing evidence is insufficient or conflicting to establish the efficacy or clarify the risk/benefit).[24] The exact impact on the treatment of these patients is unknown, but given that reimbursement for PLEX can now be tested, it is likely to be significant. Given the importance of this issue, it is imperative to understand the study that resulted in this change in practice, especially since questions have been raised about its methodology.[25]

The randomized controlled trial by Clark *et al.*[21] was the third and largest randomized controlled trial looking at the effect of PLEX on myeloma associated renal failure. Despite its randomized controlled design, several serious limitations can potentially alter its outcomes and conclusions. First of all, in a small study with negative results, it is often difficult to determine whether the negative results were due to ineffectual therapy or an underpowered study. The power was further compromised by the use of a composite outcome, which considered death of any cause and eGFR $<30\,\mathrm{ml\,min^{-1}}\,1.73\,\mathrm{m^{-2}}$ a failure. The significance of $30\,\mathrm{ml\,min^{-1}}1.73\,\mathrm{m^{-2}}$ in the composite outcome is unclear. While the effect of dialysis dependence on survival has been demonstrated, there is no evidence to suggest that an eGFR of $<30\,\mathrm{ml\,min^{-1}}\,1.73\,\mathrm{m^{-2}}$ is associated with poorer prognosis in myeloma patients.[1,2,5,19] And while an eGFR of $<30\,\mathrm{ml\,min^{-1}}\,1.73\,\mathrm{m^{-2}}$ is certainly clinically significant, it still represents a tremendous improvement in the quality of life over dialysis. Dialysis dependence also limits the most advanced therapies because of protocols and/or bias and may contribute to the poorer survival. However, the most serious limitations of the study had to be the lack of renal disease confirmation and a therapeutic marker. The deficiency in renal biopsies and the lack of a therapeutic marker made it impossible to determine the disease being treated and the adequacy of treatment. Despite the multicenter, randomized controlled design, these limitations seriously undermined their results and conclusions.

In this study, PLEX was found to be effective at reversing renal failure if it was due to CN and if sFLC levels can be reduced by at least 50%. When both criteria were met, renal function improved in 78% of the patients. The renal function did not improve in any CN patient whose sFLC could not be reduced by 50%. This relationship was only significant in patients with CN. In patients with other renal pathology, the recovery of renal function did not depend on sFLC reduction. Improvement in renal function was seen despite $<50\%$ reduction of sFLC, whereas $>50\%$ reduction did not insure renal recovery. This finding may explain the differences in outcomes reported by the three randomized trials especially in the latest study where biopsy was rarely performed and no marker of therapy was used.[19–21]

The result of this study showed that confirmation of the diagnosis was a key factor in the success of therapy. While reduction of free light chains was important, only patients with CN responded to PLEX in a predictable manner. Renal biopsy was necessary in order to confirm the diagnosis. No association was found between CN and sFLC levels although no CN was seen in patients with sFLC <157 mg per 100 ml. Urine protein and M-spike were even less helpful having neither positive nor negative predictive values. Our data are consistent with previous studies in which $>1/3$ of our patients biopsied did not have CN.[9,10,15] This reinforces our belief that any study that does not confirm the diagnosis with renal biopsy should be interpreted with caution. Histological features may also be helpful in prognostication as patients with CN and chronic tubulointerstitial changes did not respond to treatment. This is consistent with previous observations.[6] Renal biopsy was safe in our population. The concern that renal biopsy is risky in this population appears unsupported.

In this study, PLEX did not reduce sFLC in an expected manor. Thus, studies that arbitrarily assign the number of treatments in advance may be under-treating some patients. Instead, PLEX should be guided by sFLC levels to avoid under- and over-treatment. In addition, the variable reduction of sFLC by PLEX highlights the importance of chemotherapy. Refractoriness to PLEX most likely reflects the high rate of light-chain production and myeloma activity. In this situation, effective chemotherapy can significantly slow the production light chains, whereas PLEX can enhance

its removal, which is impaired by the renal failure. One could argue that with effective chemotherapy PLEX may be unnecessary. However, response to PLEX was noted in patients who did not receive chemotherapy. In addition, response to any particular chemotherapy regimen cannot be predicted and may be delayed. PLEX can provide a bridge until an effective chemotherapy can be delivered or take effect. This is important since chronicity of renal failure can affect the degree of recovery.

There were several limitations we would like to point out in our study. First, as a retrospective study the treatments received were not controlled. Neither the chemotherapy nor PLEX was uniformly applied. In those who were found not to have CN, PLEX was discontinued without regard to sFLC level. This opens the argument that non-CN patients may require a different level of sFLC reduction in order achieve renal response. While this is certainly possible, the non-responders without CN actually had the lowest posttreatment sFLC level (50.6 mg per 100 ml), which was far below the median (312 mg per 100 ml) attained by the responders in that group. Another limitation is the differences between our patients and those of the previous randomized trials. More patients from Zucchelli's study and Johnson's study were dialysis dependent (82.8 and 57.1%, respectively) than the ones from this study (22.5%) and in Clark's study (29.9%).[19–21] However, pathologically our patients were more similar to the patients in Johnson's and Zucchelli's study, whose renal diagnosis was confirmed by renal biopsy in 76 and 59%, respectively. This could not be determined for patients in the Clark's study, since they were rarely biopsied. And unlike Clark's study, which required a baseline Scr within 30 days of the study, the duration of renal failure could not be determined for 32.5% of our patients. Fortunately, presence of a historical Scr did not affect renal response. Finally, this small retrospective study limits the strength of the evidence.

In conclusion, our study suggests that PLEX may still be beneficial in the treatment of cast nephropathy. We agree that PLEX has no role in the treatment of undifferentiated renal failure in patients with multiple myeloma.[21] However, our small study suggests that when cast nephropathy can be confirmed, renal recovery seems to be highly associated with significant sFLC reduction. This relationship was recently reported by others using a large pore dialyzer to remove pathologic light chains from patients with cast nephropathy.[26] The large-pore dialyzer is currently not available in the United States, but it supports our observation that more rapid sFLC reduction is beneficial in cast nephropathy. This relationship definitely deserves further studies, as sFLC may provide the key target for therapy in cast nephropathy. Future study design should incorporate three elements, (1) tissue confirmation of cast nephropathy, (2) a set target for the sFLC reduction instead a preset number of plasma exchanges, and (3) a single highly effective chemotherapeutic regimen. Patients should be hydrated while waiting for biopsy results to rule out pre-renal causes. These elements would insure diagnosis and therapeutic equivalency, thus isolating PLEX as the independent variable. Although still preliminary, the results of this study and others give a new enthusiasm that extracorporeal removal of light chains may be beneficial in the treatment of cast nephropathy. Validation may come yet for plasma exchange after over three decades.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board at the Mayo Foundation, in accordance with the Declaration of Helsinki Principles and the Health Insurance Portability and Accountability Act (HIPPA) guidelines. The Transfusion Medicine Therapeutic Apheresis Unit records were examined for patients with a diagnosis of multiple myeloma who underwent plasma exchange between January 2002 and June 2006. The number of plasma exchanges, laboratory values, demographic data, and additional treatments were extracted from our electronic databases.

sFLC was measured by nephelometry using the BN II nephelometer (Dade Behring, Deerfield, IL, USA) and Freelite Serum Free Light Chain Assays (The Binding Site Inc., San Diego, CA). The internal coefficient of variance for κ-light chain was 7.9% at 0.05 mg per 100 ml and 7.9% at 34 mg per 100 ml. For λ-light chain, the coefficient of variance was 10% at 0.05 mg per 100 ml and 2.6% at 43 mg per 100 ml. Total protein and urine monoclonal (M) spike were obtained from urine protein electrophoresis. Renal biopsies were obtained under real time ultrasound guidance and were processed for light microscopy, immunofluorescence and electron microscopy. Congo red staining was performed based on the history, histological features, or at the request of the physician.

PLEX was performed with the COBE Spectra (Gambro BCT, Lakewood, CO, USA) running version 7 software. One plasma volume exchange was performed daily to every other day. Sodium citrate was used as the anticoagulant and the plasma volume was replaced with 5% albumin. Fresh frozen plasma was used if an invasive procedure was planned. PLEX was usually performed via central vascular access. Initially, patients usually received five exchanges unless complications prevented further treatment. Later, exchanges continued until sFLC was below 200 mg per 100 ml. PLEX was deemed ineffective and was discontinued if the sFLC level could not be altered after five exchanges. Dialysis was performed based on the usual criteria. Renal biopsy was obtained at the discretion of the nephrologist. The choice of chemotherapy was determined by the hematologist.

Multiple myeloma was defined by lytic bone lesions or bone marrow plasmacytosis $>10\%$. Renal failure was defined as a Scr 50% above the baseline or $\geqslant 2.0$ mg per 100 ml if baseline is unavailable. eGFR rate was calculated using the Modification of Diet in Renal Disease Study (MDRD) equation.[27] Patients who were dialysis dependent were assigned an eGFR of 0. Exposure to non-steroidal anti-inflammatory drugs and other nephrotoxins was recorded. In this study, renal response was defined as a 50% reduction of presenting Scr and dialysis independence at 180 days.

Statistical analysis was performed using JMP version 6.0.0 (SAS Institute Inc., Cary, NC, USA). Pearson's χ^2-tests were performed on categorical data. Two-sample *t*-tests and Wilcoxon rank-sum tests were used to compare continuous variables between groups. A logistic regression model with age, sex, renal biopsy results, presenting Scr, initial sFLC, posttreatment sFLC, number of plasma exchanges, and chemotherapy was used to identify an association with renal response. Survival was analyzed using the Kaplan–Meier method.

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