Current Trends of Renal Impairment in Multiple Myeloma

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Key Words

Multiple myeloma · Renal impairment · Haematological response · Renal response/survival

Abstract

Background: Renal impairment (RI) is a common complication of multiple myeloma (MM). Around 50% of patients with MM have RI at presentation, and up to 5% require dialysis treatment. Severe acute kidney injury (AKI) as a cause of RI is a particular challenge as historically the survival of patients who sustain this complication and require dialysis is very poor. However, in this current period, survival is improving and the focus is on optimum use of novel chemotherapies and the evaluation of extra-corporeal therapies for removal of serum immunoglobulin light chains. **Summary:** RI in patients with MM is commonly associated with excess monoclonal free light chain (FLC) production; myeloma cast nephropathy is the predominant renal pathology in patients presenting with severe RI secondary to AKI. The majority of patients have mild to moderate RI and recover renal function. However, patients with more severe RI, in particular those with a requirement for dialysis, are less likely to recover renal function. Rapid diagnosis and prompt institution of anti-myeloma therapy is an important determinant of renal

function recovery, through targeting early and sustained reduction of involved monoclonal FLC. Novel agents are associated with excellent disease response, and bortezomib is now widely used as a first-line agent in the management of MM in patients with severe RI. Extended haemodialysis using high cut-off dialysers is more effective for extracorporeal removal of FLC than plasma exchange, and clinical trials are in process. High-dose chemotherapy with autologous stem cell transplantation does have a role in patients with severe RI but requires careful patient selection. **Key Messages:** RI is very common in patients with MM, and renal function recovery is associated with improved clinical outcomes. We summarise the epidemiology of MM in the UK, present the impact of RI and renal function recovery on patient outcome, and describe the current management of MM in western countries. **Facts from East and West:** (1) A serum creatinine level >2 mg/dl has been reported in 16, 21, 24, and 33% of patients with MM in cohort studies from Japan, Europe, China, and Korea, respectively. A creatinine clearance rate <30 ml/min was observed in 30 and 15% of patients in Chinese

For the prevalence and management of multiple myeloma-induced kidney disease in China, see Shi et al., *Kidney Dis* 2015;1:235–240.

and Western MM cohorts, respectively. The commonest cause of severe RI in patients with MM is myeloma cast nephropathy. (2) The efficacy of novel treatments (bortezomib, carfilzomib, thalidomide, and lenalidomide) has predominantly been assessed in Western patients. Bortezomib and dexamethasone are the current standard of care for MM and severe RI in the West. Severe RI is not a contraindication to autologous stem cell transplantation (ASCT). Most of the data are from the West; there are case reports from China describing good outcomes with ASCT. The removal of FLC by high-cut-off hemodialysis is under evaluation in randomized controlled trials (RCTs) in the West. Studies in this area are not yet conducted in China. In China, new treatments, such as bortezomib, are more widely used than before, and favorable results are being reported; however, RCT studies are still needed in this area to confirm the efficacy and safety of this and other novel treatments.

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Introduction

Multiple myeloma (MM) is a cancer of plasma cells and has an incidence of around 50 cases per million population (pmp)/year. Fifty percent of patients have renal impairment (RI) at presentation, and up to 20% have severe acute kidney injury (AKI). Severe AKI is usually a consequence of myeloma cast nephropathy (MCN), caused by high levels of immunoglobulin free light chain (FLC). The presence of severe AKI is an important complication of MM as it is associated with an increased risk of early mortality; however, the impact of mild-to-moderate RI at presentation on patient outcome is unclear. Recent advances in chemotherapy have led to better overall survival (OS) and for patients who require dialysis as a consequence of MM, increased recovery rates of independent renal function are being reported, and these improved renal outcomes are associated with better OS.

Epidemiology

MM is the 23rd most common cancer worldwide and accounted for 0.8% of all cancer diagnoses and 1.0% of all cancer-related mortality in 2012 [1]. In the UK, it is the 17th most common cancer and accounted for 1% of all new cases in 2011, with 4,792 patients with a new diagnosis of MM. The overall UK age-standardised annual incidence is 55 pmp [2]. The incidence rises with age, and in the UK 43% of all new cases were diagnosed in individu-

als ≥ 75 years old [2]. MM is more common in males (56%) than females (44%), with a male-to-female ratio of 6:5. The cancer is twice as common in African-Americans than Caucasians, and a similar ethnic pattern is also noted in the UK [3]. The UK age-standardised mortality rate for MM is 28 deaths pmp/year. The age-standardised mortality rates decreased by 19% in the periods from 1987 to 1989 and 2010 to 2012 for males and 16% for females. Most of these improvements in outcome have occurred in the last decade; this in part reflects better diagnostics, more effective chemotherapy and improved coding practices [2].

The Definition of RI in MM

In 2003, the CRAB criteria (elevated Calcium level, Renal insufficiency, Anaemia and Bone lesions) were introduced to standardise the definition of end-organ damage associated with symptomatic MM. A serum creatinine level of $>173 \mu\text{mol/l}$ (or $>2 \text{ mg/dl}$) was the cut-off for RI [4]. The Greek Myeloma Study Group subsequently utilised this threshold to report an incidence of 21% in a cohort of 756 patients presenting with MM [5]. However, this threshold does not include the majority of patients if conventional criteria to classify RI are used. For reporting RI in clinical outcome and clinical intervention studies, a number of definitions have been used. These are summarised in table 1.

The lack of standardisation of reporting of renal function in patients with MM is an important shortfall. Converting serum creatinine into estimated glomerular filtration rate (eGFR) illuminates the potential for inaccuracy. For example, a 65-year-old female with a creatinine level above $87 \mu\text{mol/l}$ will have RI as defined by an eGFR $<60 \text{ ml/min}$ [stage 3 chronic kidney disease (CKD)]; for a male of the same age, the stage 3 CKD threshold is $113 \mu\text{mol/l}$. When RI is defined based on the threshold set by the CRAB criteria, the same 65-year-old female will have an eGFR $<25 \text{ ml/min}$ that is equivalent to stage 4 CKD; whereas for a male of the same age, the eGFR cut-off is $<34 \text{ ml/min}$.

A major additional confounder is that equations that have been developed for renal function estimation in CKD are being used for measurement of renal function in patients with AKI, with the International Myeloma Working Group recommending criteria for the diagnosis of RI in MM based on the four-variable Modification of Diet in Renal Disease (MDRD) [6] or the CKD-Epidemiology Collaboration 2009 (CKD-EPI 2009) equation [7,

Table 1. Historic definitions and incidence of RI in published studies

Study	Year	Cases	Definition and incidence of RI
Dawson et al. [130]	1971	166	out of 128 patients where blood urea level was available at diagnosis, 57 (44.5%) had serum urea levels >50 mg/dl
Kyle [131]	1975	869	serum creatinine >1.3 mg/dl in 55% of patients
MacLennan et al. [18]	1989	1,205	serum creatinine >130 μ mol/l in 42% of patients that included 12% with serum creatinine >200 μ mol/l and 10% with serum creatinine >300 μ mol/l
Rayner et al. [132]	1991	141	serum creatinine $\geq$ 120 μ mol/l in 65 (46%) patients that included 52 (80%) with serum creatinine 120–500 μ mol/l and 13 (20%) with serum creatinine >500 μ mol/l
Knudsen et al. [133]	1994	1,353	serum creatinine $\geq$ 130 μ mol/l in 416 (31%) patients that included 16% with severe RI defined as a serum creatinine >200 μ mol/l; CrCl was calculated in 1,206 patients – mild RI was observed in 296 (25%), moderate in 175 (15%) and severe in 115 (9%)
Kyle et al. [134]	2003	1,027	serum creatinine >1.3 mg/dl in 48% of patients that included 19% with serum creatinine $\geq$ 2 mg/dl
Eleutherakis-Papaïakovou et al. [5]	2007	756	serum creatinine $\geq$ 2 mg/dl in 160 (21%) of the 756 of patients that included 7% of patients with serum creatinine $\geq$ 4 mg/dl, 4% with serum creatinine $\geq$ 6 mg/dl, and 1% with serum creatinine $\geq$ 8 mg/dl

8]. The large majority of patients with MM and RI at presentation have AKI not CKD.

Furthermore, creatinine-derived equations can be confounded by other factors relevant to patients with MM [9–12]; these include changes in muscles mass, dietary intake and proximal tubular dysfunction [13–15]. Recent studies have indicated that serum cystatin-C is superior to creatinine in assessing early RI, including patients with MM [16, 17]. An elevated cystatin-C level (>0.95 mg/l) was reported in 90 (57.3%) of 157 newly diagnosed patients with MM, whereas a high creatinine level (>1.4 mg/dl in men and >1.2 mg/dl in women) was detected only in 37 (23.5%) patients, with 97 (61.7%) patients demonstrating a creatinine clearance (CrCl) <80 ml/min [17].

The Relationship between Renal Function and Survival in MM

An early Medical Research Council (MRC) myelomatosis trial reported a higher number of deaths (39%) within 100 days of recruitment in patients with a serum urea $\geq$ 15 μ mol/l, or creatinine $\geq$ 200 μ mol/l if the urea was <15 μ mol/l, at diagnosis. Patients presenting with RI had an OS of 380 days with 28% survival at 2 years, compared to 52% for the entire study population at the same time point [18]. RI was responsible for 28% of the early deaths

in a subsequent analysis that combined data from the MRC IV to MRC VIII trials that excluded a large proportion of patients presenting with severe AKI [19]. A total of 3,107 patients from the MRC myelomatosis trials between 1980 and 2002 were eligible to participate in this study.

A recent retrospective study from 15 Swedish hospitals reported a significantly inferior OS in patients with RI (eGFR <60 ml/min) compared to those who did not have RI. The survival of patients with RI who were treated with bortezomib-based chemotherapy (60 months) was better than survival of those who received conventional agents (27 months) [20]. Mayo Clinic investigators reported a complete renal response rate in a higher proportion of patients treated with novel agents compared to conventional treatment. Improvement of renal function was associated with better OS, although still inferior to patients with no RI at diagnosis [21].

A number of studies have reported on outcomes in patients with MM who required dialysis, a complication sustained by approximately 5% of patients at diagnosis [22–24]. The frequency of this complication may be decreasing. In a recent study that reported on 1,773 consecutive unselected patients with newly diagnosed MM between 1991 and 2011, the incidence of patients requiring dialysis was lower (3.5%) for those diagnosed after 2005 compared to the other three time cohorts: 5.5% for 2000–2004, 6% for 1995–1999, and 5% for 1990–1994 [25].

Fig. 1. Typical appearance of an MCN: tubules containing eosinophilic proteinaceous cast with a fractured appearance and surrounding cellular reaction.

Dialysis has a major impact on the prognosis of patients with MM. A median survival of 10.2 months was reported in a single-centre study, where 82% of patients received dialysis at presentation; only 17% subsequently recovered independent renal function, these patients had a significantly better OS compared to those who remained dialysis dependent [26]. These results are comparable to data from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), with a median survival of 0.91 years for patients with MM or light chain deposition disease, compared to 4.46 years for those who did not have either of these diagnoses [27].

Recent single-centre studies are reporting improved renal recovery rates of around 60% in patients who require dialysis, and an associated improvement in survival [28]. These reports are not yet confirmed in larger prospective multicentre studies.

Pathogenesis of RI in MM

The association of MM with infection, dehydration, hypercalcaemia and bone pain leading to prescription of non-steroidal anti-inflammatory drugs, produces factors either singly or in combination that can cause AKI stage 1 and stage 2 [29]. The large majority of patients with this level of RI at presentation are likely to recover renal function. Whether this recovery is to the previous baseline is not known; we are not aware of any studies that have assessed this.

An involved FLC clone with a serum level in excess of 500 mg/l has the potential to cause severe RI secondary to MCN [28, 30, 31]. Where patients with MM and severe

AKI have undergone renal biopsy, up to 90% are reported as showing MCN [30]; this is the characteristic disease-specific renal lesion. The typical histopathologic appearance is of an eosinophilic, fractured, proteinaceous distal tubular cast consisting of monoclonal FLC and Tamm-Horsfall protein (uromodulin) along with tubulointerstitial inflammation often accompanied by a proximal tubular injury (fig. 1).

However, many patients with a serum FLC (sFLC) >500 mg/l have normal renal function, highlighting the heterogeneity of the involved monoclonal light chain for cast formation. This reflects the variability in the complementarity-determining region-3 (CDR3) of the light chain in binding Tamm-Horsfall protein [32]. In some patients, MCN is triggered by a co-factor consistent with animal models that demonstrated that hypercalcaemia, acidosis and use of diuretics all lowered the threshold for cast formation.

There are a number of other renal lesions that can be associated with MM, including AL amyloidosis, monoclonal immunoglobulin deposition disease and light-chain proximal tubulopathy presenting as Fanconi syndrome [29, 33, 34]. There is a major overlap amongst these disorders, and there are reports of some patients with MM having multiple renal pathologies.

Recovery of Renal Function and Clinical Outcomes

In an early study that included 94 patients with RI defined as a creatinine level $\geq 177 \mu\text{mol/l}$, renal recovery occurred in 26% and was associated with improved survival compared to those who did not recover renal function. A

creatinine level $<354 \mu\text{mol/l}$, calcium level $\geq 2.88 \text{ mmol/l}$ and a lower urinary light chain excretion ($<1 \text{ g/day}$) were independently associated with renal function recovery [22].

Since the widespread adoption of dexamethasone as a standard component of chemotherapy regimens for patients with MM and RI, better rates of renal recovery are being reported. A single-centre series that consisted of 41 patients with newly diagnosed MM reported renal function improvement in 73% at a median of 1.9 months in patients who received high-dose dexamethasone, either with or without a novel agent. The introduction of novel agents has further improved the potential for renal recovery. Reversibility of RI was seen in 80% at a median of 0.8 months in patients who were treated with dexamethasone and a novel agent [35].

The relationship between disease-specific response as measured by sFLC levels and renal recovery is of great interest. A study from two specialist centres reported a cohort of patients presenting with a median eGFR of 9 ml/min with 62% of patients requiring dialysis. A 60% reduction in sFLC at day 21 was associated with increased likelihood of renal recovery; 71% of patients either became independent of dialysis or had an improvement in renal function from presentation. The median survival in patients who recovered independent renal function was 42.7 months compared to 7.8 months in patients who did not recover renal function [28].

The current consensus definition for a renal response in patients presenting with less severe RI was introduced by Ludwig and colleagues [36]. These criteria are based on changes in eGFR calculated by the 4-variable MDRD equation. A complete renal response (CRrenal) is defined as a sustained (at least 2-month) improvement in baseline eGFR from <50 to $\geq 60 \text{ ml/min}$; partial renal response (PRrenal), a sustained improvement in baseline GFR from <15 to $30\text{--}59 \text{ ml/min}$; minor renal response (MRrenal), a sustained improvement in baseline GFR from <15 to $15\text{--}29 \text{ ml/min}$ or from $15\text{--}29$ to $30\text{--}59 \text{ ml/min}$.

The renal response criteria were validated in a study which compared the efficacy of a bortezomib-based chemotherapy regimen in 46 consecutive patients with MM and RI. A renal response was reported in 59%, with 30% achieving a CRrenal and with a higher probability of response amongst those with light chain-only MM. When cystatin-C was used to measure renal function, patients with levels of $>2 \text{ mg/l}$ or a cystatin-C calculated eGFR $<30 \text{ ml/min}$ had a lower probability of achieving a CRrenal response [37].

A single-centre study reported on 96 previously untreated MM patients, who were divided into three groups based on their chemotherapy regimen. Thirty-seven patients were treated with conventional agents, 47 received a thalidomide/lenalidomide-based regimen and 17 received a bortezomib-based regimen. A sustained renal response was recorded in 94% of patients treated with a bortezomib-based regimen, 79% treated with thalidomide/lenalidomide regimen and 59% treated with conventional chemotherapy [38]. Several other studies have reported on the efficacy of novel agents when used as first-line chemotherapy for the management of patients with MM and RI [30, 39–41].

Management

Medical Management

AKI in MM is a medical emergency. Optimal management comprises early institution of anti-myeloma therapy along with good supportive care. Accurate assessment of fluid balance is required; if volume depleted, treatment with intravenous fluids should be commenced immediately. Intravenous hydration along with alkalinisation of urine has shown to increase the solubility of the involved light chain clone and prevent the formation of intratubular casts [18, 42].

NSAIDs, aminoglycosides, contrast agents, angiotensin-converting enzyme inhibitor, angiotensin-II receptor blocker and loop diuretics should be stopped and further prescriptions avoided; these agents are associated with an increased risk of developing MCN. Hypercalcaemia is very common, and bisphosphonates can be used for the treatment of elevated calcium levels [43–45].

Treatment of Myeloma

Historically, treatment options for MM with RI were limited, and drug combinations with cytotoxic agents such as melphalan and cyclophosphamide in patients with RI were associated with significant toxicities. Patients presenting with severe AKI were usually excluded from clinical trials of therapy; the evidence for this group of patients is therefore derived from post hoc subgroup analyses or from trials performed in patients with relapsed MM. However, management of patients with MM has evolved considerably over the last two decades, and novel agents are now the backbone of contemporary anti-myeloma therapy (table 2).

Table 2. Published studies of novel agent-based regimen in myeloma patients with RI

Study	Year	Number of patients with RI	Requiring dialysis	Disease status	Chemo-therapy	Myeloma response	Renal response
<i>Bortezomib-based studies</i>							
Jagannath et al. [58]	2005	52 (CrCl ≤50 ml/min, with 10 patients with CrCl ≤30 ml/min)	0	relapsed or refractory	V or VD	overall response (CR + PR + MR) was seen in 25%	not reported
Malani et al. [60]	2006	4 (creatinine >3 mg/dl)	0	de novo and relapsed or refractory	V or VD	near CR – 3 (75%) and PR – 1 (25%)	improvement in renal function in all patients, with 3 patients demonstrating creatinine <2 mg/dl
Chanan-Khan et al. [61]	2007	24 (creatinine >2 mg/dl)	23	relapsed or refractory	V; VD; VTD; VAT, and other combinations	overall response (≥PR) seen in 75%; that included CR – 5 (25%), near CR – 1 (5%), and PR – 9 (45%); MR – 1 (5%)	4 (16%) patients became dialysis independent
Ludwig et al. [62]	2007	8 (CrCl <20 ml/min)	5	de novo and relapsed or refractory	V; VD; VAD	CR or near CR – 3 (37.5%), VGPR – 1 (12.5%), and PR – 1 (12.5%)	5 (62.5%) patients achieved reversal of RI; with creatinine ≤2 mg/dl – 2 (25%) and creatinine <3 mg/dl – 3 (37.5%) patients
Blade et al. [63]	2008	193 (CrCl <60 ml/min those with CrCl ≤30 ml/min were excluded)	0	relapsed or refractory	PLD + V vs. V	≥PR – 43 (49%) patients in PLD + V group; ≥PR – 39 (42%) patients in V group	improvement in renal function in both treatment groups, with slightly better response in those on PLD + V
San-Miguel et al. [59]	2008	62 (CrCl ≤50 ml/min; included 45 (14%) with CrCl 30–50 ml/min and 17 (5%) with CrCl <30 ml/min)	0	relapsed or refractory	V	overall response (≥PR) seen in 23 (40%) patients; that included CR – 4 (7%) and PR – 19 (33%)	not reported
San-Miguel et al. [55]	2008	185 (CrCl <60 ml/min)	0	de novo	VMP	CR – 28%	not reported
Roussou et al. [64]	2008	20 (CrCl ≥2 mg/dl)	5	de novo and relapsed or refractory	VD; VTD; VAD; VMTD	overall response (≥MR) seen in 65%; that included CR – 1 (5%), PR – 11 (55%), and MR – 1 (5%)	reversal of RI (creatinine <1.5 mg/dl) was seen in 8 (40%) patients; 1 of the 5 patients became dialysis independent
Dimopoulos et al. [65]	2009	111 (eGFR ≤50 ml/min; included 92 patients with eGFR 31–50 ml/min and 19 with eGFR ≤30 ml/min)	0	de novo	VMP	overall response seen in 68% that included 31% achieving a CR	renal function reversal (eGFR >60 ml/min) seen in 49 (44%) patients that included 42 (37.8%) patients with eGFR 30–50 ml/min and 7 (6.3%) with eGFR ≤30 ml/min at presentation
Dimopoulos et al. [37]	2009	46 (eGFR <50 ml/min)	9	de novo and relapsed or refractory	VD; VTD; VAD; VMTD	≥PR – 29 (63%)	overall renal response seen in 27 (59%) patients that included CRrenal – 14 (30%), PRrenal – 5 (11%), and MRrenal – 8 (17%); 2 of the 9 patients became dialysis independent
Li et al. [66]	2009	18 (creatinine ≥2 mg/dl)	5	de novo	VD-T	overall response (≥PR) seen in 83.3%; that included CR – 6 (33.3%), near CR – 3 (16.6%), VGPR – 3 (16.6%), and PR – 3 (16.6%)	overall renal response defined as 50% reduction in serum creatinine level was seen in 7 (38.9%) patients; 1 of the 5 patients became dialysis independent
Qayum et al. [67]	2010	6 (CrCl <30 ml/min)	3	de novo and relapsed or refractory	V; VD	CR – 2 (33.3%) and PR – 3 (50%)	renal function improved in all patients, with 3 (50%) patients achieving CrCl ≥60 ml/min
Morabito et al. [68]	2010	117 (eGFR <80 ml/min; included 12 (10.3%) with eGFR 51–80 ml/min, 23 (19.7%) with eGFR 30–50 ml/min and 82 (70.1%) with eGFR <30 ml/min)	14	de novo and relapsed or refractory	VD; V combined with other agents	overall response (≥PR) seen in 83 (73%) patients; that included CR – 23 (19%), near CR – 8 (8%), VGPR – 19 (17%), and PR – 33 (29%)	reversal of RI (normalisation of eGFR) was seen in 41%; 3 of the 14 patients became dialysis independent
Roussou et al. [38]	2010	17 (CrCl <50 ml/min)	altogether, 9 patients from the 3 treatment arms were on dialysis	de novo	VD	≥PR – 82%	≥PRrenal – 82%; 2 out of the 9 patients recovered renal function, both were on bortezomib
Ludwig et al. [40]	2010	68 (CrCl <50 ml/min)	9	de novo and relapsed or refractory	VAD	overall response (≥MR) seen in 72%; that included CR or near CR – 38%, VGPR – 15%, PR – 13%, and MR – 6%	overall renal response was seen in 62%, that included CRrenal – 31%, PRrenal – 7%, and MRrenal – 24%; 3 of the 9 patients became dialysis independent
Morabito et al. [69]	2011	149 (eGFR ≤50 ml/min; VMPT-VT – 70 patients and VMP – 79 patients)	0	de novo	VMPT-VT vs. VMP	overall response (≥PR) was 93.2% in VMPT-VT arm and 83.0% in VMP arm	reversal of RI (eGFR >60 ml/min) was seen in 25.4% of patients in VMPT-VT arm and 40.3% in VMP arm; time to renal function reversal was not significantly different between the 2 arms

Table 2 (continued)

Study	Year	Number of patients with RI	Requiring dialysis	Disease status	Chemo-therapy	Myeloma response	Renal response
Costa et al. [70]	2012	14 (CrCl <50 ml/min)	0	de novo	VCD	≥PR – 14 (100%) that included CR in 57.1%	overall renal response seen in 10 (71.4%) of the 14 patients; that included CRrenal – 5 (35.7%), PRrenal – 4 (28.5%), and MRrenal – 1 (7.1%)
Dimopoulos et al. [50]	2013	43 (eGFR ≤60 ml/min)	6	de novo	VD; VTD; VCD	≥PR – 81%	≥PRrenal – 33 (77%) patients, that included 29 (67.4%) patients with CRrenal; 3 of the 6 patients became dialysis independent
Yang et al. [72]	2013	30 (creatinine ≥2 mg/dl)	12	de novo	VTD	overall response (≥PR) seen in 80%; that included CR – 6 (20%), VGPR – 8 (26.7%), and PR – 10 (33%)	10 (33%) patients achieved reversal of renal function; 8 of the 12 patients became dialysis independent
Dimopoulos et al. [71]	2013	58 (eGFR <50 ml/min)	0	relapsed or refractory	VD; VCD; VDR	among those achieving a renal response ≥PR seen in 14 (58.3%) patients	overall renal response seen in 24 patients (41%), that included CRrenal – 13 (22.4%) and MRrenal – 11 (18.9%)
Scheid et al. [73]	2014	81 (creatinine ≥2 mg/dl; included 45 patients in VAD ^a -T arm and 36 patients in VAD-V arm)	0	de novo	VAD ^a -T VAD-V	overall response (≥PR) was seen in 49% of patients with RI; those on VAD ^a -T arm achieved an overall response in 36% of patients compared to 75% of those on VAD-V arm	overall renal response in VAD ^a -T arm was 63% and in the VAD-V arm was 81%
Breitkreutz et al. [74]	2014	13	13	de novo	VAD	overall response (≥PR) prior to ASCT was 83.3%, which improved to 100% after ASCT	after induction with VAD, 38.5% became dialysis independent, with a further 15.4% recovering renal function after ASCT
Gimius et al. [56]	2015	27 (eGFR <60 ml/min)	0	de novo	VD	not reported separately for patients with RI	52% had an improvement in eGFR of >20% from baseline
<i>Thalidomide-based studies</i>							
Fakhouri et al. [135]	2004	7 (CrCl <50 ml/min)	1	relapsed or refractory	TD or T alone	CR – 3 (42.8%), PR – 1 (14.2%) and MR – 3 (42.8%)	out of the 5 patients with CrCl <30 ml/min, 2 (40%) patients progressed to RRT and the remaining 3 (60%) patients maintained CrCl <30
Tosi et al. [91]	2004	20 (serum creatinine >130 μmol/l and CrCl <60 ml/min)	2	relapsed or refractory	TD or T alone	≥PR – 9 (45%)	12 (60%) patients achieved renal function recovery, i.e. serum creatinine <130 μmol/l
Tosi et al. [90]	2010	31 (CrCl <50 ml/min)	7	de novo	TD	≥PR – 23 (74%) that included 3 (10%) patients with CR and 5 (16%) with VGPR	17 (55%) patients achieved CrCl >50 ml/min; 2 out of the 7 patients became dialysis independent
<i>Lenalidomide-based studies</i>							
Niesvizky et al. [136]	2007	14 (CrCl <40 ml/min)	0	de novo	RD	not reported	3 (21.4%) out of the 14 patients improved renal function with CrCl >40 ml/min
Dimopoulos et al. [137]	2010	12 (CrCl <50 ml/min)	1	relapsed or refractory	RD	≥PR – 7 (58%)	5 (42%) of 12 patients demonstrated improvement in renal function that included CRrenal – 3 (25%) and MRrenal – 2 (17%)
Dimopoulos et al. [99]	2010	98 (CrCl <60 ml/min; included 16 patients with CrCl <30 ml/min)	0	relapsed or refractory	RD	overall response (≥PR) seen in 54 (55%) patients that included CR – 14 (14.2%), VGPR – 14 (14.2%), and PR – 26 (26.5%)	amongst those with CrCl <60 ml/min, renal function improvement was demonstrated in 72% of patients
de la Rubia et al. [100]	2010	15	15 (2 patients were on RRT prior to myeloma diagnosis)	relapsed or refractory	RD	overall response (≥PR) seen in 9 (60%) patients; that included CR – 4 (26.6%), VGPR – 1 (6.6%), and PR – 4 (26.6%)	1 patient became dialysis independent
Klein et al. [103]	2011	33 (moderate to severe RI defined as CrCl <50 ml/min)	5	relapsed or refractory	RD	overall response (≥PR) seen in 16 (48.5%) patients that included CR – 1 (3%), VGPR – 3 (9%), and PR – 12 (36.3%)	28.6% demonstrated improvement in renal function
Oehrlein et al. [102]	2012	26 (CrCl <60 ml/min; included 11.5% with CrCl <30 ml/min)	3	relapsed or refractory	RD	overall response (≥PR) seen in 21 (84%) patients that included CR – 1 (4%), and PR – 20 (80%)	overall renal response seen in 11 (42%) patients; that included CRrenal – 6 (23%), PRrenal – 1 (4%), and MRrenal – 4 (15%); all the 3 patients achieved dialysis independence
Hou et al. [138]	2013	62 (CrCl <60 ml/min; included 50 (26.7%) with CrCl 30–59 ml/min and 12 (6.4%) with CrCl <30 ml/min)	0	relapsed or refractory	RD	≥PR – 42% in patients with CrCl 30–59 ml/min ≥PR – 41.7% in patients with CrCl <30 ml/min	not reported

Table 2 (continued)

Study	Year	Number of patients with RI	Requiring dialysis	Disease status	Chemo-therapy	Myeloma response	Renal response
Tosi et al. [101]	2013	20 (CrCl <50 ml/min that included 11 (55%) patients with CrCl <30 ml/min)	4	relapsed or refractory	RD	CR – 1 (5%), VGPR – 1 (5%), PR – 6 (30%), and MR – 4 (20%)	CRrenal – 4 (20%) and PRrenal – 3 (15%), 1 patient achieved dialysis independence
Dimopoulos et al. [50]	2013	28 (eGFR ≤60 ml/min)	0	de novo	RD or MPR	overall response (≥PR) seen in 23 (82%) patients	major renal response (≥PRrenal) seen in 12 (43%) patients that included 10 (36%) patients with CRrenal
Ludwig et al. [105]	2015	35 (eGFR <50 ml/min)	13	de novo and relapsed or refractory	RD	overall response seen in 24 (68.6%) patients that included CR – 7 (20%), VGPR – 3 (8.6%), and PR – 14 (40%)	renal response seen in 16 (45.7%) patients that included CRrenal – 5 (14.2%), PRrenal – 4 (11.4%), and MRrenal – 7 (20%); 5 patients achieved dialysis independence
Yamasaki et al. [139]	2015	15 patients (median eGFR 38.5 ml/min before lenalidomide treatment)	2	relapsed or refractory	RD	≥PR – 15 (100%) that included CR – 2 (14%), VGPR – 1 (7%), and PR – 12 (80%)	post-treatment median eGFR 49.7 ml/min

PRrenal = Partial renal response; MRrenal = minor renal response; V = bortezomib; VD = bortezomib and dexamethasone; VTD = bortezomib, thalidomide and dexamethasone; VAT = bortezomib, adriamycin and thalidomide; PLD + V = pegylated liposomal doxorubicin and bortezomib; VMP = bortezomib, melphalan and prednisolone; VAD = bortezomib, adriamycin and dexamethasone; VMPT-VT = bortezomib, melphalan, prednisolone, thalidomide followed by bortezomib and thalidomide maintenance; VCD = bortezomib, cyclophosphamide and dexamethasone; VDR = bortezomib, dexamethasone and lenalidomide; VAD* = vincristine, adriamycin and dexamethasone; T = thalidomide; TD = thalidomide and dexamethasone; MPR = melphalan, lenalidomide and prednisolone.

Dexamethasone

Glucocorticoids exert a cytotoxic effect on myeloma cells by inhibiting nuclear factor- κ light chain enhancer of activated B cells (NF- κ B) and interleukin (IL)-6 [46–48]. Dexamethasone is a potent steroid that has been used both alone and in combination with other agents. In a study that included 112 newly diagnosed MM patients, a 75% reduction in serum M-protein was reported in 43% of patients treated with intermittent courses of dexamethasone. The response rate to dexamethasone used as a single agent was approximately 15% less than that of a vincristine-doxorubicin-dexamethasone (VAD) combination in a previous study, which implied that the majority of the anti-myeloma response by VAD regimen was due to dexamethasone alone [49].

In another study, high-dose dexamethasone with a novel agent was associated with a shorter length of time to renal response compared to high-dose dexamethasone in combination with conventional agents [35]. A similar finding was reported in a further study where treatment with high-dose dexamethasone (≥160 mg/month) was used in combination with thalidomide-based, bortezomib-based or lenalidomide-based regimens [50].

Proteasome Inhibitors

Bortezomib

Bortezomib is a first-in-class selective and reversible 26S proteasome inhibitor with proven efficacy in newly diagnosed MM and in relapsed or refractory MM. It targets the ubiquitin-proteasome pathway and promotes the proliferation and survival of all cells, in particular cancer cells [51]. It decreases myeloma cell binding to bone marrow stromal cells and blocks NF- κ B-mediated synthesis of IL-6 by stromal cells [52]. It has anti-angiogenic properties and inhibits vascular endothelial growth factor and IL-6 secretion by the endothelial cells [53]. Among other effects, bortezomib can modulate intracellular signalling mechanisms and gene expression to protect the renal proximal tubular cell from the anti-apoptotic effects of NF- κ B [54]. It is metabolised primarily in the liver via cytochrome P450 enzymes, and no dose alteration is necessary in patients with RI. The commonest side effects are peripheral neuropathy and haematological toxicity; electrolyte abnormality, mood disturbances, hypotension and gastrointestinal disturbances can also occur.

A subgroup analysis of the Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisolone (VISTA) trial reported no difference in CR rate (28%), time to progression and the OS in

the 185 patients with CrCl <60 ml/min compared to the remaining 159 patients who had no RI from the bortezomib arm [55].

A recent phase II study that evaluated the efficacy and tolerability of an alternate dosing regimen for bortezomib in newly diagnosed patients with MM ineligible for stem cell transplantation reported an improvement in renal function in 52% of patients with an eGFR <60 ml/min at diagnosis. The weekly bortezomib regimen was well tolerated by the elderly and frail cohort of patients, with majority of the adverse events reported to be of grade 1/2 severity; only 1 patient in this study developed a grade 3/4 peripheral neuropathy from bortezomib therapy [56].

In another study, subcutaneous bortezomib was an effective alternative in relapsed MM compared to intravenous therapy in a multicentre phase III trial that showed comparable efficacy in the overall response rate, time to progression and 1-year OS in the two treatment groups. RI defined as CrCl ≤60 ml/min at presentation was present in 41% of patients who received subcutaneous and in 32% who had intravenous bortezomib. Patients on subcutaneous bortezomib had lower grade 3 or worse adverse events than those on intravenous treatment (57 vs. 70%, respectively) [57].

A retrospective pooled analysis of the Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy (SUMMIT) and the Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma (CREST) investigated the response rate and safety of bortezomib in recurrent and/or refractory MM in patients with severe RI as defined by a CrCl of 10–30 ml/min. Ten patients were reported, of whom 6 also received dexamethasone. Overall response was noted in 3 patients (30%); 2 patients achieving partial response (PR) and 1 patient achieving a minimal response (MR). This was one of the earliest studies to report on the clinical benefit of bortezomib in this high-risk group of patients [58].

A subgroup analysis of the Assessment of Proteasome Inhibition for Extending Remissions (APEX) study also studied bortezomib in relapsed MM. Patients treated with bortezomib had a superior disease response (≥PR 38 vs. 18% in CrCl >50 ml/min group; 40 vs. 16% in ≤50 ml/min group) and longer time to progression (6.2 vs. 3.5 months in CrCl >50 ml/min group; 4.9 vs. 2.8 months CrCl ≤50 ml/min group) compared to treatment with high-dose dexamethasone. Adverse event rate was comparable for each group for bortezomib; however, a higher frequency of adverse events and drug discontinuation was seen in

the dexamethasone arm [59]. A number of other studies [37, 38, 40, 50, 59–74] have reported on bortezomib in patients with RI; these are summarised in table 2.

Carfilzomib

Carfilzomib is a new generation proteasome inhibitor approved in the United States for patients with relapsed and/or refractory MM. The PX-171-005 study evaluated the safety and efficacy of carfilzomib in 50 patients with relapsed and/or refractory MM and included 18 (36%) patients with CrCl <50 ml/min and an additional 8 (16%) patients on dialysis. There was no impact of RI on the clearance of carfilzomib. A PR or greater response occurred in 23.5% of patients with a CrCl <50 ml/min and in 37.5% of those on dialysis, 1 of whom achieved renal function recovery and became dialysis independent [75]. An analysis of 4 separate phase II studies that totalled 526 patients, including 23.8% with a CrCl <50 ml/min, demonstrated no worsening in renal function in 86.8% following treatment with carfilzomib; 13.2% had at least one episode of RI and with grade 3/4 adverse events as a consequence occurring in 7.2% [76].

Immunomodulatory Therapy

Thalidomide

Thalidomide was the first immunomodulatory agent to show promise in the treatment of MM. The drug has anti-angiogenic, anti-inflammatory and anti-immunomodulatory properties [77]. Specific effects include blockade or down-regulation of TNF-α, cyclooxygenase-2 and myeloma cell targeted stromal derived factor-1α and its receptor CXCR-4 [78, 79]. Thalidomide undergoes biotransformation by non-enzymatic hydrolysis in the liver to form multiple metabolites with <1% excretion of these metabolites in the urine [80, 81].

Thalidomide has limited haematological toxicity, and can therefore be used both as a single agent and in combination with other chemotherapeutic agents [82–86]. The pharmacokinetics in patients receiving dialysis has not been extensively studied, and there are reports of hyperkalaemia in patients with RI [77, 87]. The most common side effects are peripheral neuropathy that is usually encountered after a prolonged exposure [88], and thromboembolic events. The risk of thromboembolism increases when used in combination with other agents, especially high-dose dexamethasone [89]. Despite over 15 years of clinical use, there is a disappointingly low quantity of useful data on thalidomide in RI.

The efficacy of thalidomide-dexamethasone prior to autologous stem cell transplantation (ASCT) in previous-

ly untreated patients presenting with a CrCl of <50 ml/min was reported by Tosi et al. [90]. They noted a $\geq$ PR in 74% of patients that included 26% with a very good partial response (VGPR). An improvement in renal function after induction occurred in 82% of patients with a $\geq$ PR, compared to 37% in those who did not achieve a PR.

In a study of 20 consecutive advanced, refractory or relapsed patients with MM and RI (including 3 patients requiring dialysis) treated with thalidomide alone or in combination with dexamethasone, a PR was noted in 9 patients and an MR in 6 additional patients. Renal function recovery occurred in 12 of 15 patients who responded to treatment; thalidomide alone was associated with a maximal disease response at a median of 6 weeks, and thalidomide plus dexamethasone at a median of 4 weeks. The toxicity of thalidomide as monotherapy or in combination with dexamethasone was similar to that observed in patients with MM and normal renal function [91].

Lenalidomide

Lenalidomide is a second-generation immunomodulatory agent which has direct tumoricidal activity in MM [92–95]. The kidney is the primary route of elimination, with 84% of the drug secreted in the urine in patients with normal renal function. Therefore, clearance of lenalidomide decreases with a progressive decline in renal function; from 69% in patients with a CrCl 50–80 ml/min, to 38% in patients with CrCl 30–49 ml/min, and 43% in patients with CrCl <30 ml/min. In moderate to severe RI or end-stage kidney disease, the area under the concentration-time curve increases by approximately 185–420%, and the median half-life increases by 6–12 h; furthermore, a single session of 4-hour haemodialysis only removes 31% of the administered dose [96]. As a result, dose recommendations in patients with MM and RI are in place [97]. Lenalidomide therapy is associated with an increased risk of thromboembolic events [91], and neutropenia and thrombocytopenia are also important side effects [98].

Lenalidomide and dexamethasone were assessed in patients with RI in the MM-009 and MM-010 multicentre, phase III clinical trial; 71, 24 and 5% had a CrCl of $\geq$ 60, 30–59 and <30 ml/min, respectively. There was no significant difference in the overall response, time to progression and progression-free survival between groups. However, patients with a CrCl <30 ml/min had a shorter survival (18.4 months) than those with a CrCl 30–59 ml/min (29.0 months) or CrCl $\geq$ 60 ml/min (38.9 months). A renal response occurred in 72%. Thrombocytopenia and

discontinuation of lenalidomide (mainly due to cytopenia) was more common in those with severe RI [99].

de la Rubia et al. [100] reported the use of lenalidomide and dexamethasone in 15 refractory and/relapsed MM patients on dialysis. Thirteen patients received lenalidomide three times a week after dialysis treatment at a dose of 15 mg/day, and 2 patients received lenalidomide at a dose of 5 mg/day and 5 mg on alternate days, respectively. 29% achieved a CR, 7% a VGPR and 29% a PR. One patient who achieved a PR attained independence from dialysis. Haematological toxicity was common; 53% of patients required a reduction in the dose of lenalidomide due to the development of cytopenia. This study showed that with careful monitoring and with appropriate dose adjustments, lenalidomide could be used for relapsing or refractory MM in patients requiring dialysis. Overall, the results of studies to date indicate that lenalidomide therapy is an important treatment option in the management of MM in patients with RI [101–105].

Pomalidomide

Pomalidomide is another new-generation immunomodulatory agent used in combination with dexamethasone for the management of relapsed and/or refractory MM. The superiority of pomalidomide with low-dose dexamethasone compared to pomalidomide alone or high-dose dexamethasone alone was reported in a phase II [106] and a phase III [107] study, respectively; however, individuals with moderate to severe RI at presentation were excluded from both studies. It is metabolised extensively via multiple pathways, with <5% of the administered pomalidomide dose excreted unchanged in the urine. Studies to assess the efficacy and safety of pomalidomide in patients with severe RI are currently underway [108].

Autologous Stem Cell Transplantation

High-dose chemotherapy followed by ASCT is an established treatment option for MM. RI had no impact on stem cell collection and post-transplant engraftment in small single-centre studies [109, 110], with some centres reporting cases of recovery from requiring dialysis [110, 111].

High-dose melphalan (200 mg/m²) is associated with excessive toxicity; when the dose of melphalan was reduced to 140 mg/m² in a study where 21 of the 81 patients had advanced RI (creatinine >177 μ mol/l with 47% on dialysis), transplant-related mortality was observed in 6 and 13% of patients after single and tandem ASCT, respectively. Dialysis dependence and melphalan dose did

Table 3. Published studies of use of HCO haemodialysis in myeloma patients with severe RI

Study	Year	Patients on RRT	Disease status	Renal biopsy findings	Chemotherapy	Myeloma response	Renal response
Hutchison et al. [121]	2007	5	de novo	MCN	dexamethasone-based regimen	not reported	3 (60%) achieved dialysis independence
Hutchison et al. [30]	2009	19	16 patients – de novo 3 patients – relapsed	MCN	cyclophosphamide – 7; thalidomide – 14; vincristine + doxorubicin – 1; dexamethasone – all patients	not reported; however, sustained FLC reduction noted in 13 (68.4%) patients	14 (73.6%) patients achieved dialysis independence
Peters et al. [140]	2011	5	de novo	MCN	VD	not reported; however, a mean FLC reduction of $90 \pm 6\%$ seen after the third session of HCO dialysis, with an FLC reduction of $61 \pm 20\%$ per session over 2 weeks	3 (60%) patients became dialysis independent
Sinisalo et al. [125]	2012	7	de novo	available in 6 (85.7%) patients, all demonstrating MCN	VD – 3; VD + MP – 1; VD + VAD ^a – 1; RVD – 1; VTD – 1	not reported	6 (85.7%) patients achieved dialysis independence
Hutchison et al. [39]	2012	67	50 patients – de novo 17 patients – relapsed	available in 38 (56.7%) patients with 86.7% demonstrating MCN	novel agent used in 56 patients	42 (61%) patients had a reduction in FLC levels; amongst these, 83% had a $\geq 50\%$ decline in FLC levels by day 21	42 (63%) patients achieved dialysis independence
Heyne et al. [127]	2012	19	10 patients – de novo 9 patients – relapsed or refractory	available in 6 (31.5%) patients, all demonstrating MCN	novel agent used in 14 patients	$\geq \text{PR} - 6$ (42.8%)	14 (73.7%) patients achieved dialysis independence
Khalafallah et al. [124]	2013	4	3 patients – de novo 1 patient – relapsed	unknown if renal biopsy performed	VAD – 2; VD – 1 TD – 1 (switched to RD)	$\geq \text{VGPR} - 3$ (75%) patients	3 (75%) patients achieved dialysis independence
Tan et al. [141]	2014	6	de novo	MCN	VCD – 3; CTD – 1; CD – 2	$\geq \text{PR} - 4$ (66.6%)	3 (50%) patients achieved dialysis independence
Zanetti et al. [122]	2015	21	de novo	15 (71.4%) patients demonstrating MCN	VTD – 13 (ASCT eligible) VMP – 8 (ASCT ineligible)	sCR – 4 (19%), VGPR – 10 (48%), and PR – 3 (14%)	16 (76%) patients achieved dialysis independence

RRT = Renal replacement therapy; PRrenal = partial renal response; MRrenal = minor renal response; VD = bortezomib and dexamethasone; MP = melphalan and prednisolone; VAD^a = vincristine, adriamycin and dexamethasone; RVD = lenalidomide, bortezomib and dexamethasone; VTD = bortezomib, thalidomide and dexamethasone; VAD = bortezomib, adriamycin and dexamethasone; TD = thalidomide and dexamethasone; RD = lenalidomide and dexamethasone; CD = cyclophosphamide and dexamethasone; VCD = bortezomib, cyclophosphamide and dexamethasone; CTD = cyclophosphamide, thalidomide and dexamethasone; VMP = bortezomib, melphalan and prednisolone; sCR = stringent complete response.

not affect event-free survival or OS [112]. In a subsequent study in dialysis patients, a further reduction in melphalan dose (100 mg/m^2) produced a similar toxicity profile, transplant-related mortality, disease response and OS compared to patients with no RI [113].

Published data around the disease and renal response in patients with advanced RI are variable. In a single-centre study of 59 patients requiring dialysis, ASCT was associated with independence of dialysis in 13 of 54 patients who survived more than 30 days. A shorter duration of dialysis (≤ 6 months), achievement of a CR or near CR and $\text{CrCl} \geq 10 \text{ ml/min}$ were all associated with recovery of independent kidney function [114].

More recently, Mayo clinic investigators reported long-term outcomes following ASCT in 30 patients with advanced RI (creatinine $>3 \text{ mg/dl}$); 15 patients were receiving dialysis, and only 1 recovered renal function. The non-dialysis patients had a modest improvement in eGFR from 15 to 19 ml/min. CR was noted in 14 patients. Although patients who achieved a CR had a better median

eGFR than those who did not, the authors found no association between haematological response and baseline eGFR with renal outcome [115].

Current guidelines support the idea that ASCT is an attractive treatment option in the management of MM; however, careful patient selection is required, especially in patients with advanced RI [116].

Role of Extra-Corporeal Removal of FLC

Therapeutic Plasma Exchange

The largest randomised control trial in patients with MM and severe AKI recruited between 1998 and 2003 failed to show a beneficial effect of plasma exchange (PE) on patient and renal outcomes; the limitations of this study included the lack of a renal biopsy confirming a diagnosis of MCN and the absence of serum or urinary light chain measurement [117].

Subsequently, Leung et al. [118] investigated the efficacy of PE in 40 patients with MM and severe RI that included 9 (22.5%) patients on dialysis. A renal response

was noted in 18 (45%) patients, which included 14 patients with MCN who had sFLC levels measured before and after treatment with PE. Of these 14 patients, an sFLC reduction of $\geq 50\%$ was reported in 64.3%; 7 of these patients had a significant renal response. Two (22%) patients subsequently became dialysis independent. The authors concluded that PE for extra-corporeal FLC removal only had a role in biopsy-proven MCN and in patients who demonstrated a $\geq 50\%$ reduction in sFLC levels from baseline.

However, PE as an isolated treatment does not provide clinical benefit, and the improvements in clinical outcome associated with a $\geq 50\%$ reduction in FLC in this study most likely reflect a chemosensitive FLC clone. As FLC have a molecular weight of 25–50 kDa and are distributed in both the intra- and extravascular compartments, a single session of PE removes $<10\%$ of extracellular FLC. The current consensus is that FLC removal by PE is unlikely to contribute to improving patient outcome [119, 120] and the present focus is on high cut-off (HCO) haemodialysis, which has greater efficacy for FLC removal than PE.

HCO Haemodialysis

Hutchison et al. [121] performed a series of in vitro and in vivo studies to assess the efficacy of several protein-leaking haemodialysers and developed a theoretical model and clinical strategy for extra-corporeal FLC removal in patients with MM presenting with severe RI. From the dialysers tested, the Gambro™ HCO 1100 with a molecular weight cut-off in vivo of around 65 kDa was found to be highly efficient for FLC removal. The model found that extended (8–12 h) daily dialysis would accelerate reduction in sFLC levels provided that the involved FLC was chemo-responsive.

A pilot study reported outcomes in 19 patients with MM who received dialysis for severe AKI, using the HCO 1100 membrane. Thirteen patients who had uninterrupted courses of chemotherapy and extended dialysis demonstrated a sustained FLC reduction, reflecting single-session reductions of 69% in κ -FLC and 71% in λ -FLC levels. Twelve (86%) of the 14 patients who became dialysis independent also had an early and sustained reduction in sFLC levels; median time from presentation to dialysis independence was 24 days. Median survival in patients who had uninterrupted chemotherapy was significantly better compared to those who had treatment suspended due to potential complications [30].

A further report from a multicentre study assessed the relationship between FLC level and renal function in di-

alysis-dependent patients treated with HCO haemodialysis and chemotherapy. The majority of patients in this study received a novel chemotherapeutic agent. A $\geq 50\%$ reduction in sFLC level was seen in 68% of patients by day 12 and in 83% of patients by day 21. The majority of patients who demonstrated early reduction in sFLC level also became dialysis independent. Patients who did not achieve independence from dialysis were more likely to have sustained a delay in initiating HCO haemodialysis treatment. In a multivariable model, the factors that were associated with independence from dialysis were FLC reduction at day 12 and day 21 and time to initiating HCO haemodialysis [39].

There are several other small studies which have highlighted the benefit of HCO haemodialysis in renal function recovery in patients with MM and severe RI (table 3) [122–127]; however, supplementation of HCO haemodialysis to current standard of care in assisting renal outcome and in doing so long-term patient outcome needs to be carefully investigated, and hence results of the European trial of free Light chain removal by exTended haemodialysis in cast nephropathy (EuLITE) and studies in patients with MM and renal failure due to MCN (MYRE) are awaited [128, 129].

Future Directions

The outcomes in patients with MM and RI are improving, and newer classes of agents including antibodies (e.g. anti-SLAMF7 – elotuzumab, anti-CD38 – daratumumab) and histone deacetylase inhibitors (e.g. panobinostat and vorinostat) have shown great promise in phase II/III studies, and it would be reasonable to expect the improved myeloma response rates that are being sustained with these agents to lead to better renal outcomes for patients with MM who have RI.

There are several research questions that can stratify the management of patients with MM and RI in the next decade. These include: better defining the relationship between FLC level and renal function at diagnosis; describing the relationship between FLC response and renal function in patients who do not require dialysis at presentation, and understanding the impact of mild-to-moderate RI on long-term patient outcome. Finally, patients with severe RI are usually excluded from major intervention trials; future studies need to address this to improve the evidence base of novel and next-generation therapies.

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Conflict of Interest Statement

The authors declare no conflict of interest.

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