The Prevalence and Management of Multiple Myeloma-Induced Kidney Disease in China

Hao Shi Zijin Chen Jingyuan Xie Nan Chen

Department of Nephrology, Ruijin Hospital, and Institute of Nephrology, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Key Words

Bortezomib · China · Diagnosis · Multiple myeloma · Renal impairment

Abstract

Background: Multiple myeloma (MM) is a clonal B-cell malignancy of the bone marrow. Renal impairment is a common complication of MM. So far, there is no systematic overview of MM-induced kidney disease in China. **Summary:** The incidence of MM is 0.6/100,000 in China. Twenty-four, 19.7, and 30.8% of all patients with MM had renal insufficiency [defined by serum creatinine (Scr) ≥ 2 mg/dl] at diagnosis in China mainland, Hong Kong and Taiwan, respectively. Novel criteria based on the estimated glomerular filtration rate measurements are recommended for the assessment of renal function in patients with MM with stabilized Scr. It is reported that 78% of the MM patients had a creatinine clearance rate (Ccr) < 90 ml/min, and 30.5% had a Ccr < 30 ml/min. The IgG type was the most prevalent in MM patients; the light-chain and IgD type usually had a higher rate of kidney damage than others. New more effective drugs, blood purification technology and peripheral blood autologous stem cell transplantation have been introduced in clinical practice. Unfortunately, the studies conducted in the patients

with renal insufficiency were almost all retrospective, had a small sample size and a short follow-up time. Although new treatments such as bortezomib are more widely used than before, traditional chemotherapy is still used, also because of economic constraints. The RIFLE criteria, which seem to be appropriate to define the severity of acute kidney injury (AKI), have been extensively validated worldwide but rarely in patients with MM. It was the first time to apply the RIFLE system to analyze the natural history of MM patients with AKI retrospectively in our unit. The severity of AKI defined by using the RIFLE criteria (OR = 2.04, $p = 0.06$) was associated with a marginal better long-term outcome. **Key Messages:** Novel criteria of renal insufficiency should be introduced into practice when treating MM. The treatment of MM patients with kidney disease has been greatly improved recently. It is necessary to conduct further large randomized controlled trials of the long-term outcome in China. **Facts from East and West:** (1) An Scr level > 2 mg/dl has been reported in 16, 21, 24, and 33% of patients with MM in cohort studies of Japan, Europe, China, and Korea, respectively. A Ccr < 30 ml/min was observed in 30 and 15% of patients in Chinese and West-

For current trends in renal impairment in multiple myeloma, see Yadav et al., Kidney Dis 2015;1:241–257.

ern MM cohorts, respectively. The commonest cause of severe renal impairment (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 free light chain by high cutoff 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.

© 2016 S. Karger AG, Basel

Introduction

Multiple myeloma (MM) is a clonal B-cell malignancy of the bone marrow associated with a variety of clinical manifestations, including renal impairment, anemia, bone disease and infection. Myeloma cast nephropathy is the major cause of renal failure in MM, which results from precipitation of monoclonal light chain (LC) with Tamm-Horsfall protein into casts that occlude renal distal tubule lumens. In addition to myeloma cast nephropathy, several glomerulopathies are associated with MM, including LC amyloidosis (AL) and monoclonal immunoglobulin deposition disease (MIDD). Nephrotic syndrome and chronic renal failure were more prevalent in these patients. AL is characterized by Congo-red-positive deposits of LC (predominantly lambda LC), which consisted of nonbranched arranged fibrils with an external diameter of 10–12 nm. MIDD is present as amorphous granular monoclonal immunoglobulin deposits along the tubular, glomerular and vascular basement membranes under immunofluorescence or electron microscopy. MIDD includes LC deposition disease (LCDD), predominantly deposits of kappa LC, heavy-chain deposition disease and light- and heavy-chain deposition disease.

MM accounts for 1% of all kinds of malignancies and is the second most common hematological malignancy. The estimated incidence of MM is roughly 120,000 per year worldwide, and the median age at diagnosis is 70 years [1]. The incidence of MM is 0.6/100,000 in China, which is much lower than that in Africa (12.7/100,000).

Moreover, MM ranks the third in China after leukemia and non-Hodgkin's lymphoma among all hematologic malignancies [2, 3].

About 15–40% of all MM patients have renal function insufficiency. The assessment in these studies varied greatly because of inconsistencies in the definition of renal injury [4–11]. Around 30–40% of the MM patients had a serum creatinine (Scr) level above the normal range at diagnosis. The Asia Myeloma Network (including 3,405 MM patients) reported that 23.4% of the MM patients had renal function insufficiency (defined by Scr >2 mg/dl) at diagnosis. In this study, this percentage is 24% in China mainland, 19.7% in Hong Kong, 30.8% in Taiwan, 16.1% in Japan (the lowest) and 33.5% in Korea (the highest) [12]. Zhao et al. [13] reported that 78% of the MM patients had a creatinine clearance rate (Ccr) <90 ml/min, and 30.5% had a Ccr rate <30 ml/min.

The incidence of MM in end-stage renal disease patients from the USA is 1.0%, while the prevalence rate in the same population is 0.3% [14]. Data from the ERA-EDTA showed that the incidence of MM-related end-stage renal disease increased from 0.7 pmp in 1986–1990 to 2.52 pmp in 2001–2005 [15]. However, we lack relevant data for China.

Clinical Characteristics and Diagnosis

Patients with IgG and IgA MM-induced kidney diseases mainly present with renal tubular injury and renal failure, while renal AL or LCDD is rare. Interestingly, patients with LC and IgD MM usually have a higher rate of kidney damage than others. Apart from tubular damage, glomerular injury is also common, which eventually leads to renal AL or LCDD and presents with nephritic syndrome. Renal failure occurs in nearly 50% of all LC MM. Although the incidence of IgD MM is only 1%, over 90% of the IgD MM patients have renal failure. According to the study by Kim et al. [12], patients with IgG, IgA, IgD, LC and nonsecretory MM accounted for 55.2, 22, 3.1, 17.9, and 1.9% of all heavy-chain type MM patients from Asia, respectively. In Hong Kong, Chow et al. [16] reported that 22.2% of the MM patients had renal insufficiency at diagnosis onset; renal insufficiency was most prevalent in the LC type. In our kidney department, out of 211 MM patients, 40.8% had IgG MM, 20.9% IgA MM, 7.6% IgD MM and 20.9% LC MM. The renal insufficiency rate was 62.8, 59, 75 and 86.4%, respectively. The nephrotic syndrome ratio was 10.5, 15.9, 18.8 and 9.1%, respectively. On 61 patients (28.9%), renal biopsy was performed; 26 patients

had cast nephropathy, 9 AL, 2 LCDD, 3 acute tubulointerstitial nephritis and 5 had chronic tubulointerstitial nephritis. Other histological findings included focal segmental sclerosis, diffuse mesangial proliferation with sclerosis, and minimal-change disease. Extrarenal biopsies including mandibular mass/lymph node, rectal mucosa and tongue were performed and AL was confirmed in 5 patients. Most MM patients with kidney involvement presented as classical cast nephropathy. According to our experience, renal biopsy does not need to be performed routinely; however, it is useful to identify glomerular lesions in patients with urinary albumin >1 g/24 h, or to estimate the severity of the renal tubulointerstitial nephritis and predict the reversible possibility of the renal impairment, or to assess the main cause of the renal failure.

MM should be suspected in the following situations: (1) age >40 with unknown cause of renal insufficiency; (2) the degree of anemia and renal damage is not proportional; (3) nephritic syndrome without hematuria, hypertension, or early stage of kidney disease with anemia and renal failure; (4) renal insufficiency with hypercalcemia; (5) increased erythrocyte sedimentation rate, hypergammaglobulinemia and infection (e.g. urinary tract and respiratory tract), and (6) inconsistent results of proteinuria by urine routine test and 24-hour urine protein test.

Currently, the criteria by Durie and Salmon [17] (established in 1975) and the International Staging System (established in 2005) [18] are still widely used. β_2 microglobulin and albumin are convenient and reliable markers; thus, they are suggested by the International Staging System for stage classification. The definition of renal injury according to the Durie-Salmon criteria, i.e. Scr >2 mg/dl, is debatable with its potential underestimation of renal injury. Guidelines for the estimation of renal injury and treatment for MM-related kidney disease are not available currently. Due to inconsistency, the results from different studies are not comparable. Recently, to standardize the definition of MM with kidney damage, new chronic kidney disease (CKD) and acute kidney injury (AKI) guidelines have been proposed. For kidney damage in CKD and AKI, several important criteria have been suggested, including: (1) using the MDRD formula and CKD-EPI formula to calculate estimated glomerular filtration rate (GFR), and staging kidney damage by the 2013 KDIGO CKD guideline [19]; (2) AKI could be diagnosed by RIFLE [20], AKIN [21] and KDIGO AKI criteria [22] established in 2012. In our center, we retrospectively analyzed the natural history of 78 patients with MM-related AKI. It was the first time to apply the RIFLE criteria to evaluate the severity of AKI as 'risk', 'injury' and 'failure'

in MM patients. The mean Scr level was 592.7 ± 371.5 $\mu\text{mol/l}$ (range 142–1,644), and 89.7% were Durie-Salmon stage 3 at presentation. According to RIFLE, 14.1% were at a 'risk' stage, 14.1% at an 'injury' stage and 71.8% at a 'failure' stage. The severity of AKI staged by RIFLE class (OR = 2.04 failure stages vs. risk and injury stage, $p = 0.06$) was associated with a marginal better long-term outcome [23]. The inconsistency between the RIFLE and AKIN criteria is the time: 7 days in the RIFLE and 48 h in AKIN [24]. Therefore, RIFLE can be used in a retrospective study, while AKIN is more suitable for a prospective study.

Treatment

Effective treatment for MM can reduce plasma LC concentration and improve renal function in >50% of the MM patients. The aim of the treatment for MM is to get more complete remission and to prolong the progression-free survival time. Over the past decade, schemes of chemotherapy for MM have changed a lot. The use of new medicines (such as bortezomib) and peripheral blood autologous stem cell transplantation (ASCT) highly increase the remission rate and improve the prognosis. Traditional chemotherapy management of MM included melphalan and prednisone, vincristine plus doxorubicin plus dexamethasone and high-dose dexamethasone. Because of economic reasons, such therapies were still used in China.

Bortezomib is the first-in-class proteasome inhibitor that has been approved for the treatment of MM. The treatment efficiency of bortezomib is better than traditional chemotherapy. The NCCN (National Comprehensive Cancer Network) has recommended bortezomib monotherapy or combined therapy in primary and refractory MM. Bortezomib is considered safe and effective in the treatment of MM patients with renal injury at any degree, even in patients with dialysis [25]. In some phase III studies, the effect of bortezomib has been confirmed. In the VISTA study, 6, 27 and 67% of the MM patients receiving VMP (bortezomib, melphalan, and prednisone; $n = 344$) had a GFR rate ≤ 30 , 31–50 and >50 ml/min. The efficiency rate was 74, 67 and 72% [complete response (CR) 37, 29 and 30%], respectively; 44% of the patients recovered their renal function [26]. Unfortunately, in China, only retrospective studies with small sample sizes and a short follow-up time have been conducted. Li et al. [27] reported 18 newly diagnosed MM patients with renal impairment (Scr >2 mg/dl), i.e. with a mean creatinine level of 5.3 mg/dl in a prospective study. Patients received

Table 1. Comparison of studies related to the MM patients with AKI [23]

First author [Ref.], year	Total, n	Study period	Mean age, years	Definition of renal failure in original publication	AKI identified	Definition of renal recovery for the study	Outcome			
							chemo-therapy response, %	renal recovery, %	dialysis dependence, %	survival time, months
Irish [7], 1997	56	1980–1994	67	Severe renal failure (no exact definition)	Indefinite	Dialysis independent	NR	15	71	8
Bladé [6], 1998	94	1969–1994	63	Scr ≥ 177 $\mu\text{mol/l}$	Indefinite	Scr < 133 $\mu\text{mol/l}$	39	26	NR	8.6
Knudsen [4], 2000	225	1984–1992	69.5	Scr ≥ 130 $\mu\text{mol/l}$	Indefinite	Scr < 130 $\mu\text{mol/l}$	NR	58	3.6	13–18
Eleutherakis-Papaikovou [8], 2007	160	1995–2004	NR	Scr ≥ 177 $\mu\text{mol/l}$	Indefinite	NR	55	NR	NR	19.5
Prakash [9], 2009	26	1994–2007	59.3	Severe renal failure (no exact definition)	Yes	< 123 $\mu\text{mol/l}$	53	38.5	15.4 (not accurate ^a)	NR
Haynes [10], 2010	107	1987–2006	67	Severe AKI Scr ≥ 500 $\mu\text{mol/l}$	Yes	Dialysis independent	NR	17	70	10.2
Matsue [11], 2010	12	2001–2008	74	Need for dialysis	Yes	< 177 $\mu\text{mol/l}$	66.7	58	33	NR
Study of Ruijin Hospital	78	1995–2010	58	RIFLE criteria	Yes	Returned to $\pm 10\%$ of baseline kidney function	44.9	43.6	29.5	17

NR = Not reported. ^a Seven patients were lost to follow-up after 4–5 dialyses.

a median of 4 cycles of bortezomib and dexamethasone. The overall response rate of MM was 83.3%, including a 33.3% CR rate, and a 16.7% near-CR rate. Moreover, 33.3% of the patients achieved renal response (a 50% decrease in Scr, and the median time to reversal was 16 days). In a retrospective study, 56 MM patients with renal impairment received bortezomib-based chemotherapy, with a median Ccr of 25.33 ml/min [28]. The overall response rate was 82.4%, including a CR rate of 32.4%. The overall renal response was 89.3%, the CR rate was 62.5% (Ccr ≥ 60 ml/min), the partial CR rate was 14.3% (Ccr from baseline < 15 ml/min to ≥ 30 –59 ml/min) and the minor response rate was 12.5% (Ccr from baseline < 15 ml/min to ≥ 15 –29 ml/min, or from baseline 15–30 ml/min to 30–59 ml/min). The median time to renal response was 25.5 days. No significant difference in the median survival time was detected among MM patients of different renal impairment degree. The incidence of peripheral neuritis was found to be as high as 55.6%, which resulted in 10 cases who discontinued therapy. In our department, 29 patients with MM and renal impairment received bortezomib-based therapy; their mean age was 59.1 ± 9.4 years and their median creatinine level was 281 $\mu\text{mol/l}$ when admitted to hospital. Nineteen of them received ≥ 4 cycles of regimen; the CR and partial response rate of MM was 36.8 and 47.4%, respectively. The overall

renal response rate (a 50% decrease in Scr) was 84.2%, and 36.8% steadily recovered to baseline Scr level; 2 of 4 patients were dialysis-independent.

Thalidomide was the first immunoregulatory medicine for MM that proved effective. Renal impairment does not affect the pharmacokinetics; however, hyperkalemia should be monitored in patients with severe renal impairment [29]. Lenalidomide is a derivative of thalidomide, mainly excreted through the kidney, and dose adjustment was required according to the renal function: the doses should be reduced to 10 mg/day for Ccr 30–50 ml/min; 15 mg every other day for Ccr < 30 ml/min, and 5 mg/day after dialysis for dialysis patients [30]. At present, there is no randomized controlled study of these two drugs for MM patients with renal injury. There is a lack of relevant research in this population in China.

ASCT has been performed for more than 20 years, which is obviously superior to the traditional chemotherapy. With the development of protease inhibitors and immunoregulatory medicine, the new therapy based on these new medicines has achieved similar efficacy compared to ASCT. However, they cannot be a substitute for ASCT. There is no doubt of the importance of ASCT in MM treatment. Together, the use of ASCT and other new medicines can help get remission of minimal residual disease and further improve the treatment efficacy [31, 32].

ASCT combined with high-dose therapy should be regarded as one of the basic therapies for newly diagnosed MM patients aged <65 years. It is feasible for patients under dialysis or with renal injury to receive ASCT. Although ASCT could be considered in severe renal injury patients (GFR <30 ml/min), it is only recommended to be performed in an expertise center [33]. Badros et al. [34] reported that 81 MM patients with renal failure (Scr >176 $\mu\text{mol/l}$; 38 patients underwent dialysis) received ASCT as well as a large dose of melphalan. No significant difference in the CR rate and overall survival time was found between the two groups (melphalan 200 and 140 mg/m^2), but more side effects (such as lung complication and mucosal inflammation) were observed in the former group. ASCT has become increasingly popular in China, while few studies on MM patients with renal impairment have been carried out. We reported 4 cases of MM with renal involvement (2 cases of the IgG type, 1 case of the IgD type and 1 case nonsecretory), receiving ASCT treatment. Two cases had AKI, 1 case CKD stage II and 1 case CKD stage V. All 4 patients received 4–6 cycles of chemotherapy before transplantation. Of 3 patients with mild to moderate renal involvement, 2 achieved CR after ASCT, with recovery (2 cases) or stability (1 case) of the renal function. One year later, 1 case died of plasma cell leukemia, and the other 2 cases remained in complete remission. The patients with severe renal involvement (CKD stage V) died of septic shock after ASCT, although we reduced the dose of melphalan to 140 mg/m^2 [35].

Treatment of MM with kidney disease includes removing aggravating factors of renal impairment, drinking enough water, alkalinizing urine, and preventing hypercalcemia as well as hyperuricemia. Dialysis is suitable for MM patients with severe renal function. Conventional dialysis cannot get rid of LC. In vitro, high flux dialysis may effectively remove serum LC, but we still lack an evidence-based study. In vivo, the HCO1100 dialyzer, a new PAES dialyzer, was efficient for cleaning out free LC. The molecular cutoff in the blood dialyzed with the HCO1100 device is three times larger than normal high flux. If considering a longer dialysis duration together with higher dialysis frequency, a better effect would be achieved [36]. Two prospective studies (EuLITE and MYRE Study) are still in progress [37]. A case report from Hong Kong reported a Chinese woman who presented with MM and AKI due to contrast nephropathy, with extremely high serum lambda-free LC. This patient had AKI after Velcade-thalidomide-dexamethasone therapy (Scr 547 $\mu\text{mol/l}$), then received a high cutoff extended hemodialysis of 8 h per day and continued this therapy for 6 days.

The LC concentration decreased from 490 to 112 mg/l , and she stopped dialysis after 3 months [38].

Plasma exchange (PE) is found not to be effective in improving the long-term prognosis of MM patients; thus, it is not recommended as a standard treatment [39]. The largest multiple-center and open randomized controlled trial, published in 2005 by Clark et al. [40], found that PE had no significant benefits, but the incidence of dialysis dependence was twice in chemotherapy compared to PE combined therapy at 6 months. In our center, 24.4% (19/78) of the MM patients with AKI received PE. The CR rate of renal function in the PE group was higher than in the non-PE group (42.1 vs. 15.3%, $p = 0.014$), although no difference in the median survival time was seen (26 vs. 16 months, $p = 0.34$) [23].

The natural history of MM is 6–12 months, and the median survival time after chemotherapy is 3–4 years. We analyzed a group of patients with MM and AKI between 1995 and 2010, and compared them to similar studies (table 1). In our study, the median survival time was 46 months, the severity of AKI predicted renal response but not chemotherapy response, and older age (OR = 1.04, $p = 0.01$), hypercalcemia (OR = 2.57, $p = 0.01$) and reversibility of renal insufficiency (OR = 3.35 for no vs. yes, $p = 0.001$) were independent prognostic factors associated with survival [23].

Conclusion

Kidney injury is the most common complication in patients with MM. In recent years, treatment has greatly progressed. Bortezomib, showing highly increasing efficacy of treatment, prolonged survival time, and no requirement for dose adjustment in renal failure patients, is now regarded as first-line treatment. It is more widely used than before despite the relatively high cost of bortezomib and shows favorable results in China. To date, we still lack experience in ASCT in MM patients with renal failure. Hemodialysis, especially high cutoff hemodialysis, can improve the prognosis. New medicine chemotherapy combined with delayed high cutoff extended hemodialysis brings new hope for the treatment of MM patients with renal failure; however, more evidence is still needed.

Conflict of Interest Statement

We declare that we have no financial and personal relationships with other people or organizations that could have inappropriately influenced our work.

References

- Ludwig H, Miguel JS, Dimopoulos MA, et al: International Myeloma Working Group recommendations for global myeloma care. *Leukemia* 2014;28:981–992.
- Surveillance epidemiology and end results. Fast Stats: an interactive tool for access to SEER cancer statistics, Surveillance Research Program, National Cancer Institute. <http://seer.cancer.gov/faststats> (accessed May 8, 2013).
- http://globocan.iarc.fr/Pages/fact_sheets_population.aspx.
- Knudsen LM, Hjorth M, Hippe E: Renal failure in multiple myeloma: reversibility and impact on the prognosis. *Nordic Myeloma Study Group. Eur J Haematol* 2000;65:175–181.
- Kyle RA, Gertz MA, Witzig TE, et al: Review of 1,027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 2003;78:21–33.
- Bladé J, Fernández-Llama P, Bosch F, et al: Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. *Arch Intern Med* 1998;158:1889–1893.
- Irish AB, Winearls CG, Littlewood T: Presentation and survival of patients with severe renal failure and myeloma. *QJM* 1997;90:773–780.
- Eleutherakis-Papaïakovou V, Bamias A, Gika D, et al: Greek Myeloma Study Group: Renal failure in multiple myeloma: incidence, correlations, and prognostic significance. *Leuk Lymphoma* 2007;48:337–341.
- Prakash J, Niwas SS, Parekh A, et al: Multiple myeloma – Presenting as acute kidney injury. *J Assoc Physicians India* 2009;57:23–26.
- Haynes RJ, Read S, Collins GP, Darby SC, Winearls CG: Presentation and survival of patients with severe acute kidney injury and multiple myeloma: a 20-year experience from a single centre. *Nephrol Dial Transplant* 2010;25:419–426.
- Matsue K, Fujiwara H, Iwama K, Kimura S, Yamakura M, Takeuchi M: Reversal of dialysis-dependent renal failure in patients with advanced multiple myeloma: single institutional experiences over 8 years. *Ann Hematol* 2010;89:291–297.
- Kim K, Lee JH, Kim JS, et al: Clinical profiles of multiple myeloma in Asia – An Asian Myeloma Network study. *Am J Hematol* 2014;89:751–756.
- Zhao Y, Li J, Huang B, et al: Clinical evaluation of chronic renal failure in 178 patients with multiple myeloma. *Chin J Nephrol* 2008;24:761–762.
- Collins AJ, Foley RN, Chavers B, et al: United States Renal Data System 2011 Annual Data Report: atlas of chronic kidney disease and end stage renal disease in the United States. *Am J Kidney Dis* 2012;59(1 suppl 1):A7, e1–e420.
- Tsakiris DJ, Stel VS, Finne P, et al: Incidence and outcome of patients starting renal replacement therapy for end-stage renal disease due to multiple myeloma or light-chain deposit disease: an ERA-EDTA Registry study. *Nephrol Dial Transplant* 2010;25:1200–1206.
- Chow CC, Mo KL, Chan CK, et al: Renal impairment in patients with multiple myeloma. *Hong Kong Med J* 2003;9:78–82.
- Durie BGM, Salmon SE: A clinical staging system for multiple myeloma. *Cancer* 1975;36:842–854.
- Greipp PR, San Miguel J, Durie BG, et al: International staging system for multiple myeloma. *J Clin Oncol* 2005;23:3412–3420.
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO clinical practice guideline for the evaluation and management of CKD. *Kidney Int Suppl* 2013;3:1–150.
- Bellomo R, Ronco C, Kellum JA, et al: Acute Dialysis Quality Initiative workgroup: Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;8:R204–R212.
- Mehta RL, Kellum JA, Shah SV, et al: Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11:R31.
- Kidney Disease: Improving Global Outcomes (KDIGO) AKI Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012;2:1–138.
- Shi H, Zhang W, Li X, et al: Application of RIFLE criteria in patients with multiple myeloma with acute kidney injury: a 15-year retrospective, single center, cohort study. *Leuk Lymphoma* 2014;55:1076–1082.
- Cruz DN, Ricci Z, Ronco C: Clinical review: RIFLE and AKIN – time for reappraisal. *Crit Care* 2009;13:211.
- Anderson KC, Alsina M, Bensinger W, et al: National Comprehensive Cancer Network (NCCN): Multiple myeloma. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2007;5:118–147.
- Dimopoulos MA, Richardson PG, Schlag R, Khuageva NK, Shpilberg O, Kastritis E, et al: VMP (Bortezomib, Melphalan, and Prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: cohort analysis of the phase III VISTA study. *J Clin Oncol* 2009;27:6086–6093.
- Li J, Zhou DB, Jiao L, et al: Bortezomib and dexamethasone therapy for newly diagnosed patients with multiple myeloma complicated by renal impairment. *Clin Lymphoma Myeloma* 2009;9:394–398.
- Xu Y, An G, Deng Sh, et al: Clinical feature and efficacy of patients with multiple myeloma and renal impairment treated with bortezomib based chemotherapy. *Chin J Hematol* 2013;34:303–308.
- Harris E, Behrens J, Samson D, et al: Use of thalidomide in patients with myeloma and renal failure may be associated with unexplained hyperkalaemia. *Br J Haematol* 2003;122:160–161.
- Dimopoulos MA, Alegre A, Stadtmauer EA, et al: The efficacy and safety of lenalidomide plus dexamethasone in relapsed and/or refractory multiple myeloma patients with impaired renal function. *Cancer* 2010;116:3807–3814.
- Paiva B, Vidriales MB, Cervero J, et al: Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. *Blood* 2008;112:4017–4023.
- Rawstron AC, Child JA, de Tute RM, et al: Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. *J Clin Oncol* 2013;31:2540–2547.
- Smith A, Wisloff F, Samson D, et al: Guidelines on the diagnosis and management of multiple myeloma. *Br J Haematol* 2006;132:410–451.
- Badros A, Barlogie B, Siegel E, et al: Results of autologous stem cell transplant in multiple myeloma patients with renal failure. *Br J Haematol* 2001;114:822–829.
- Shi H, Zhang W, Li X, et al: Autologous peripheral blood stem cell transplantation in multiple patients with renal involvement. *J Intern Med Concepts Pract* 2011;6:356–360.
- Hutchison CA, Cockwell P, Reid S, et al: Efficient removal of immunoglobulin free light chains by hemodialysis for multiple myeloma: in vitro and in vivo studies. *J Am Soc Nephrol* 2007;18:886–895.
- Bridoux F, Fermand JP: Optimizing treatment strategies in myeloma cast nephropathy: rationale for a randomized prospective trial. *Adv Chronic Kidney Dis* 2012;19:333–341.
- Shum HP, Chan KC, Chow CC, et al: Cast nephropathy with acute renal failure treated with high cut-off haemodialysis in a patient with multiple myeloma. *Hong Kong Med J* 2010;16:489–492.
- Barosi G, Boccadoro M, Cavo M, et al: Management of multiple myeloma and related disorders: guidelines from the Italian Society of Hematology (SIE), Italian Society of Experimental Hematology (SIES) and Italian Group for Bone Marrow Transplantation (GITMO). *Haematologica* 2004;89:717–741.
- Clark WF, Stewart AK, Rock GA, et al: Plasma exchange when myeloma presents as acute renal failure. A randomized, controlled trial. *Ann Intern Med* 2005;143:777–784.