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

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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 (CrCr) <90 ml/min, and 30.5% had a CrCr <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 CrCr <30 ml/min was observed in 30 and 15% of patients in Chinese and West-
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 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 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 failure [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, hyperggammaglobulinemia 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. β2 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 μmol/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

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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. Among MM patients with renal impairment and AKI, the 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].

<table>
<thead>
<tr>
<th>First author [Ref.], year</th>
<th>Total, n</th>
<th>Study period</th>
<th>Mean age, years</th>
<th>Definition of renal failure in original publication</th>
<th>AKI identified</th>
<th>Definition of renal recovery for the study</th>
<th>Outcome chemotherapy response, %</th>
<th>renal recovery, %</th>
<th>dialysis dependence, %</th>
<th>survival time, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irish [7], 1997</td>
<td>56</td>
<td>1980–1994</td>
<td>67</td>
<td>Severe renal failure (no exact definition)</td>
<td>Indefinite</td>
<td>Dialysis independent</td>
<td>NR</td>
<td>15</td>
<td>71</td>
<td>8</td>
</tr>
<tr>
<td>Bladé [6], 1998</td>
<td>94</td>
<td>1969–1994</td>
<td>63</td>
<td>Scr ≥177 μmol/l</td>
<td>Indefinite</td>
<td>SCR &lt;133 μmol/l</td>
<td>39</td>
<td>26</td>
<td>NR</td>
<td>8.6</td>
</tr>
<tr>
<td>Prakash [9], 2009</td>
<td>26</td>
<td>1994–2007</td>
<td>59.3</td>
<td>Severe renal failure (no exact definition)</td>
<td>Yes</td>
<td>&lt;123 μmol/l</td>
<td>53</td>
<td>38.5</td>
<td>15.4</td>
<td>NR</td>
</tr>
<tr>
<td>Haynes [10], 2010</td>
<td>107</td>
<td>1987–2006</td>
<td>67</td>
<td>Severe AKI Scr ≥500 μmol/l</td>
<td>Yes</td>
<td>Dialysis independent</td>
<td>NR</td>
<td>17</td>
<td>70</td>
<td>10.2</td>
</tr>
<tr>
<td>Matsue [11], 2010</td>
<td>12</td>
<td>2001–2008</td>
<td>74</td>
<td>Need for dialysis</td>
<td>Yes</td>
<td>&lt;177 μmol/l</td>
<td>66.7</td>
<td>58</td>
<td>33</td>
<td>NR</td>
</tr>
<tr>
<td>Study of Ruijin Hospital</td>
<td>78</td>
<td>1995–2010</td>
<td>58</td>
<td>RIFLE criteria</td>
<td>Yes</td>
<td>Returned to ±10% of baseline kidney function</td>
<td>44.9</td>
<td>43.6</td>
<td>29.5</td>
<td>17</td>
</tr>
</tbody>
</table>

NR = Not reported. a Seven patients were lost to follow-up after 4–5 dialyses.
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 μmol/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 (melphanal 200 and 140 mg/m²), 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/m² [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 μmol/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 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.
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