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Renal Disease in Multiple Myeloma

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1. Introduction

Renal involvement is a common feature of Multiple Myeloma (MM) that is associated with significant morbidity and shortened survival. At the time of diagnosis, some degree of renal impairment is present in about half of the cases. In some of patients dialysis is required eventually (Hutchison, 2007). A review from the US Renal Data System (USRDS) reports that the number of patients with myeloma associated end-stage renal disease (ESRD) in 2004 in the United States was 5,390, with a prevalence of 1.1%. The presence of renal involvement is commonly associated with a higher tumor burden and worse prognosis, as the severity of renal failure is highly correlated with patient survival. Based on large series in which renal function was evaluated by serum creatinine levels; 43% of 998 patients had a renal insufficiency with the serum creatinine concentrations above 1,5 mg/dl (133 µmol/L) and one-year survival was found 80% in this group, while it was 50% in the patient group who had creatinine levels more than 2,3 mg/dl (200 µmol/L) (Winearls CG,1995). In another report, 22% of 423 patients had a severe renal insufficiency with the values of creatinine concentration greater than 2 mg/dl (177 µmol/L) (Bladé J,et al.,1998). As the serum creatinine level is affected due to the attenuated muscle mass of elderly MM patient population, International Myeloma Working Group has recommended use of glomerular filtration rate calculated by Modification of Diet in Renal Diseaese (MDRD) formula for the assessment of renal functions. For the assessment of the severity of acute renal injury, RIFLE (Risk, Injury, Failure, Loss and End-stage) and AKIN (Acute Kidney Injury Network) criteria may also be used.

Renal failure is reversible in the majority of the patients and reversibility is an important prognostic factor which is associated with a long-term survival. With appropriate therapy, more than 50% patients with moderate renal insufficiency had improvement in renal functions during the first three months and it was found to be associated with better prognosis. (Knudsen et al.,2000) Successful managment of reversible precipitating factors such as dehydration, hypercalcemia, hyperuricemia, infections and use of nephrotoxic agents like contrast materials, non steroidal anti-inflammatory drugs (NSAID) and angiotensin-converting enzyme inhibitors can successfully contribute to reversal of renal failure. Initiation of early aggressive anti-myeloma therapy results in rapid decline of light chain production which can contribute significantly to renal function recovery.

Pathogenesis of renal disease in Multiple Myeloma is multifactorial . It is associated with excess production of monoclonal light chains by the neoplastic B-cell clone. Renal lesions occur primarily in tubules; however glomeruli, interstitium and blood vessels may also be involved. Myeloma cast nephropathy (Light Chain Cast Nephropathy –LCCN, Myeloma kidney) is the most prominent type of MM renal involvement and is primarily tubular. Isolated distal or proximal tubular dysfunction and acquired Fanconi Syndrome also may be seen. Glomerular lesions are usually related to AL-amyloidosis and light/heavy deposition disease. Interstitial nephritis and plasma cell infiltration demonstrate the involvement of renal interstitium. Types of pathologic lesions are basically determined by the mutated amino acid sequence of the monoclonal light chain. This was confirmed with LC injected mice that developed the same pattern of renal disease as was seen in the donor MM patient. (Solomon A, Weiss DT, Kattine AA,1991) Autopsy series of patients with myeloma found that the most frequent pathology is LCCN accounts for 40% to 60%, whereas light chain deposition disease and amyloidosis were seen in 5% and7% cases respectively. (Ivanyi B.,1989) In native renal biopsy studies of patients with myeloma and renal disease,40 to 63% had cast nephropathy, 19 to 26% had light-chain deposition disease, 7 to 30% had amyloidosis, and <1% had cryoglobulinemic renal > disease." (Ganewal D.,et al,1992 ve Montseny JJ. et al,1998) Renal biopsy is not indicated many patients for differential diagnosis to concern therapeutic options and estimation of prognosis in patients with the diagnosis of myeloma. (Kidney biopsy is generally not indicated for many of patients)

We have tried to summarize the all pathophysiological mechanisms and clinical presentations of renal involvement in MM patients in this chapter.

2. Light Chain Cast Nephropathy (myeloma kidney)

LCCN is the most common cause of renal failure associated with myeloma, which accounts for approximately 90% of the cases. (Lin J,et al,2001) Renal failure may present both acutely or chronically but it is often acute in nature and can be severe with serum creatinine levels above 7 mg/dl (Montseny J,et al,1998). Characteristic lesion is a tubulointerstitial nephritis associated with monoclonal free light chains (FLCs) leading to intra-tubular cast formation/obstruction and direct tubular toxicity. Overproduction of FLCs by the neoplastic B-cell clone plays a crucial role in causing typical renal damage characterized by tubular atrophy and tubulointerstitial fibrosis. The degree of renal impairment correlates with tubular injury but not with the extent of cast formation. (Silva FG, et al,1983)The normal amount of light chain excretion is less than 30 mg/day, however it is generally more than 1 gr/day in a myeloma patient with LCCN and can be massive (>20 gr/day) leading to nephrotic syndrome in less than 10% of the cases. The rate of FLC excretion corelates with renal insufficiency. In a demographic study of 1353 patients, 16% of the cases with < 1 gr/d FLC proteinuria had renal failure versus 47% and 63% in those with 1-10 gr/d and > 10 gr/d, respectively (p=0,001) (Knudsen LM,et al,1994) Patients with LCCN are at higher risk of developing advanced myeloma with severe anemia and hypercalcemia (Durie-Salmon stage 3).

2.1 Pathogenesis of LCCN

The main pathology is cast nephropathy ie : the presence of excess FLCs in the plasma and urine which are produced by a neoplastic clone of plasma cells. Catabolism of circulating

FLCs intrinsically occurs in the kidney. In normal individuals, serum FLCs are relatively freely filtered through the glomerulus because of their low molecular weights (22,5 kd for monomeric kappa and 45 kd for dimeric lambda) and cationic net charge. After glomerular filtration; the FLCs in the tubular fluid bind to the tandem scavenger receptor system megalin/cubilin and are endocytosed via the clathrin dependent endosomal/lysosomal pathway (Batuman V et al., 1998). Megalin and cubilin are the two major, multiligand, endocytic receptors which are highly expressed in the apical endocytic apparatus of the renal proximal tubule and they are responsible for the tubular reabsorbtion of most proteins filtered in the glomeruli. Receptor Associated Protein (RAP) is also known as a high-affinated ligand for megalin, thus, it plays a significant role in endocytic function of the proximal tubule (Verroust PJ et al.,2002). Endocytic uptake of FLCs is followed by the hydrolisation and degradation in the lysosomes, and after acidifying in vesicles, the released aminoacids pass through basement membrane and re-circulate back to the system (Leheste et al., 1999)

In Multiple Myeloma, over-production of FLCs exceeds the reabsorbation capacity of the proximal tubules and results in the presence of FLCs in the distal nephron and overflow light chain proteinuria (Bence Jones proteinuria). Tamm-Horsfall Mucoprotein (THMP, also known as Uromodulin) is a renal epithelial glycoprotein which is secreted by the cells of the thick ascending limb of the loop of Henle and it forms the gel-like matrix of urinary casts. Over-concentrated FLCs bind to a specific peptide domain on THMP and constitutes the waxy cast formation that aggregates in distal tubules leading to tubular obstruction. Some factors may promote cast formation, such as dehydration (by stasis in tubules), hypercalcemia, acidosis, radiocontrast medications (by interacting with light chains) and furosemide (by increasing luminal sodium chloride). Increasing intra-luminal pressure reduces the glomerular filtration rate, therefore by the loss of metabolism related to GFR, circulating concentration FLCs increases also in the tubules. This circumstance triggers a vicious cycle in the pathogenesis of myeloma kidney. Intra-tubular cast formation usually results in tubular rupture and necrosis that precipitates interstitial inflammatory nephritis (Hill GS et al.,1983) Interstitial fibrosis and tubular atrophy follow : this fact can be accepted as the main pathology underlying the renal impairment related to cast nephropathy. Direct tubular toxicity is one of the another basic mechanisms leads to LCCN and dose-dependent toxicity can be occur in the proximal tubuler epithelial cells (PTEC) by light chains, resulting in tubular necrosis. Type of light chain is also important to determine the degree and the localization of renal injury for the reason that nephrotoxicity may differ based on the characteristics of the light chains. THMP interacts with the hyper-variable regions of the light chains and shows variable affinity to different types (Sanders et al., 1990). This phenomenon can explain why some patients have a severe renal disease with smaller amount of light chains and some have minimal renal dysfunction with larger rates. It is also well known that kappa and lambda light chains are both toxic to the tubule ephitelium but lambda is more associated with amyloidosis whereas kappa is frequently involves in Light Chain Deposition Disease (LCDD) and acquired adult's Fanconi's syndrome.

Recent studies in last decade put emphasis on the role of proximal tubule cells in the pathogenesis of cast nephropathy. These studies have demonstrated that proximal tubular endocytosis of light chains induces pro-inflammatory and inflammatory cytokine releasing such as IL-6, IL-8, TNF alfa and monocyte chemotactic protein-1 (MCP-1). It has also been

suggested that these cytokines and chemokines are mediated by activated transcription factors like NF-kappa β which are signalled through the MAPKs ERK 1/2, JNK and p38. (Sengul S et al., 2002,2003). This inflammatory process results in interstitial fibrosis and tubular damage which is associated most probably with the additon of incremental Transforming Growth Factor β (TGF-β) production (Keeling J, Herrera GA, 2007). There are still ongoing studies to clarify the molecular mechanisms involved in cast nephropathy and further studies are needed to have a clear understanding.

2.2 Diagnosis of LCCN

According to a renal biopsy study of 259 elderly patients who had unexplained renal failure, LCCN was found in 40% of patients with previously undiagnosed myeloma (Haas M,et al,2000). On this basis, LCCN should be considered in any patient over age 40 who presents with unexplained renal failure. Urine dipstick test is usually inadequate to detect FLCs, because it is primarily sensitive for albumin but insensitive for Bence Jones protein. Therefore, sulfosalicylic acid (SSA) which detects all proteins should be chosen to detect FLCs by the assessment of turbidity. A remarkably positive SSA test when dipstick is relatively negative supports the presence of non-albumin proteins like Bence Jones protein in the urine.Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) should be performed initially in every patient with suspected myeloma. To confirm the diagnosis by measuring the amount and type of the monoclonal protein, immunofixation of serum and 24 h urine collection are also recommended especially in patients with normal protein electrophoretic pattern in cases with strong suspicion for myeloma. FLC assays which reveal the quantification of serum FLC levels, κ/λ ratio and urinary FLC excretion should be obtained on every patient and these assays are particularly important in non-secretory myeloma patients whom serum and urine immunofixation analysis is negative.

For a definitive diagnosis, renal biopsy is generally needed. Pathologic findings of LCCN basically include the demonstration of prominent tubular casts in distal nephron. With light microscopy, in hematoxylin and eosin-stained sections, the casts are brightly eosinophilic and usually seem large and "brittle" because they are typically lamellated/fractured and also surrounded by macrophages and multinucleated giant cells of foreign-body type diagnostically. The other staining properties of the casts are classified as Periodic acid-Schiff (PAS) negative, fuchsinophilic with Masson's trichrome and less frequently Congo red positive. Immunofluorescence microscopy can differentiate the light chain with THMP from the other serum proteins.

2.3 Prognosis and treatment of LCCN

Multiple Myeloma is a progressive and incurable disease and median survival is about 6 months or less if it is not treated. In the past decade, by the advances in the myeloma treatment, median survival has increased from an average of 3 years to >5 years. Renal function is an important prognostic factor for MM and renal failure is associated with a worse prognosis as the others like lower serum albumin and higher β-2 microglobulin levels. Severity and reversibility of renal impairment is also important in prognosis. In patients who present with a plasma creatinine concentration of <1,5 mg/dl (130 μmol/L), the one-year survival was 80%, compared with 50% for patients with a creatinine level of

>2.3 mg/dl (200 μmol/L) (Winearls CG, 1995). In cast nephropathy, renal failure is often reversible by appropriate management of the precipitating factors and early aggressive treatment to reduce FLC production. Many studies suggest that renal recovery is closely related with a better prognosis and similar outcomes who have a normal renal function at diagnosis (Bladé J.et al, 1998), however, on the contrary some claims it is not associated with a favorable outcome (Kastritis et al,2007). Renal dysfunction due to LCNN is usually presents in acute nature and some factors may contribute to reduce GFR by inducing cast precipitation or may be the main cause of acute renal failure (ARF). First of all, an appropriate supportive care should be administered to correct the precipitating factors lead to ARF and it should be followed by a specific anti-myeloma therapy.

Autologous Stem Cell Transplantation in LCCN

The use of autologous stem cell transplantation (ASCT) for patients with myeloma and renal insufficiency has been studied in last decade. Many of these patients are considered ineligible for ASCT because of a high risk of treatment-related toxicity.

In a retrospective study of 81 patients with multiple myeloma and renal failure (plasma creatinine >2mg/dl), 60 patients underwent transplantation with melphalan 200 mg/m^2, and the remaining 21 had a reduction of the melphalan dose to 140 mg/m^2 because of excessive toxicity. The treatment-related mortality rate after the first ASCT was 6% and the 3-year event-free and overall survival rates were 48 and 55%, respectively. The degree of toxicity was acceptable and stem cell collection or engraftment were not negatively affected by renal failure (Badros A,et al,2001). In another large study from Mayo Clinic, it has revealed that creatinine level did not affect complete response rate and time to progression (17 months), but patients with creatinine levels above 2 mg/ml had a higher day-100 mortality rate (13% vs.3%) and a shorter overall survival rate (31 vs 47 months) than those with normal renal function. Platelet engraftment was also significantly delayed for patients with renal insufficiency. In conclusion; ASCT may reverse renal failure in patients with multiple myeloma but it must be used with caution in selected patients with an appropriate dose adjustment of melphalan.

3. Other causes of ARF and prevention and supportive care

3.1 Volume depletion

Hypovolemia facilitates cast precipitation by increasing FLC concentration in tubule lumen and lower urine flow contributes to intratubular obstruction. Some of myeloma patients present with acute oliguric renal failure and vigorous fluid therapy should be immediately initiated to replace volume depletion. The goals of fluid therapy are to increase the urine formation and tubule flow rate to prevent intratubular cast precipitation and obstruction. Isotonic or one-half isotonic saline is generally used to administer the hydration regimen with an initial infusion rate of 150 ml/h to achieve a high urine output at least 3 lt/day. Close monitoring should be carried out therefore some patients who have renal or heart failure may develop volume overload. In such cases, hydration regimen should be modified and if it is essential, a loop diuretic may be used to forced diuresis. Adequate hydration usually reverses the pre-renal component of ARF and oliguric status generally responses to therapy preferably in the first 24 hours.

3.2 Hypercalcemia

Hypercalcemia occurs in more than 25 %of myeloma patients in the course of the disease and 15 %of patients have mild hypercalcemia with serum calcium level 11.0-13.0 mg/dl at diagnosis. Moderate or severe hypercalcemia may also be seen and may contribute to ARF. Hypercalcemia is the second most common cause of renal failure in MM (Blade J, Rosinol L.,2005). As the other malignancy-related hypercalcemias, some osteoclast activating factors and bone resorbing cytokines like lymphotoxin, interleukin-6, interleukin 1-β and a parathyroid related protein are produced by neoplastic cells and results in increased bone resorption (Kitazawa R,et al,2002). Elevated calcium concentration in renal tubules cause intratubular calcium deposition and vasoconstriction in renal vasculature. Decreased glomerular filtration rate induces cast precipitation and probably augments the toxicity of FLCs (Smolens P,et al,1987). Hypercalcemia may also causes nephrogenic diabetes insipidus which is characterized by ADH resistance and with the impairment of renal concentrating ability, polyuria and polydipsia may develop. Increased diuresis results in hypovolemia and aggravates the pre-renal component of renal failure. Renal dysfunction due to hypercalcemia is usually reversible and management strategy should be based on to correct serum calcium concentration. In mild asymptomatic hypercalcemia which can be described as <14 mg/dl (4 mmol/L), initially intravenous hydration should be preferred. Loop diuretics should not be used in myeloma-related hypercalcemia because of their facilitating effect on cast nephrotoxicity by increasing luminal sodium chloride. If there is no response to the fluid therapy within 12 hours, a bisphosphonate should be administered while considering renal functions. Although bisphosphonates are very useful and effective in the management of malignancy-related hypercalcemia, they must be used with caution in myeloma patients because of their nephrotoxicity and the risk of subsequent hypocalcaemia. In addition, beside their hypocalcemic effect, it has been shown that bisphosphonates reduce the incidence of skeletal events and improve life quality (Berenson JR,et al, 1998). Pamidronate (a dose of 60 to 90 mg as a 2 hours infusion) and Zoledronic acid (a dose of 4 mg, as a 15 minutes infusion) are the most common bisphosphonates in clinical use and regimen may be repeated at intervals of 2 or 4 weeks if necessary. Serum calcium and creatinine levels should be monitorized regularly and appropriate dose adjustment should be done in patients with severe renal impairment and vitamin D deficiency. For moderate or severe hypercalcemia, anti-myeloma therapy which includes steroids should be promptly initiated. Calcitonin may also help to reduce serum calcium concentrations without the risk of severe hypocalcemia and nephrotoxicity.

3.3 Nephrotoxic drugs

Some drugs and radiocontrast materials should not be used in myeloma patients because of their nephrotoxic potential, especially in the state of volume depletion.

3.3.1 Intravenous radiocontrast solutuions

Contrast induced nephropathy (CIN) is defined as an acute reduction in renal function due to iodinated contrast media administration and it is one of the most common cause of hospital-acquired acute renal failure. Patients with myeloma are at high risk group to develop renal impairment secondary to radiocontrast using and especially in the setting

of hypovolemia, contrasts may precipitate acute renal failure in the rate of approximately 1.5 percent (McCarthy CS, Becker JA, 1992). These agents induce light chain precipitation in the tubules and furthermore they may also interact with light chains and contribute to intra-tubular obstruction. However, recent studies suggest that myeloma patients with normal creatinine and low β2-microglobulin levels (< 2.8 mg/L) are at low risk for developing CIN and radiocontrast administration is safe in this group (Pahade JK,et al,2011). Nevertheless, the removal or avoidance of iodinated contrast agents should be preferred primarily but if it is not possible, adequate hydration should be performed during and after the procedure as well as using of low-osmolar or iso-osmolar radiocontrast media.

3.3.2 Non-steroid anti-inflammatory drugs and others

NSAIDs basicly block the production of prostaglandins (PGs) via inhibition of cyclooxygenase enzyme activitiy (COX-1 and COX-2). By the suppression of vasodilatatory PGs, renal vasoconstriction occurs and it leads to a reduction in the renal blood flow and glomerular filtration rate which may contribute to ARF. PGs blockage also leads to salt and water retention by the inhibition of chloride reabsorbtion and antidiuretic hormone (ADH). NSAIDs also can develop papillary necrosis and chronic interstitial nephritis. Patients with hypercalcemia or lower renal blood flow due to congestive heart failure, chronic renal failure or any other cause of hypovolemia and sodium depletion, have higher risk for worsening renal functions after using NSAIDs (Murray MD,et al,1995). Thus, NSAID therapy in patients with myeloma should be administered carefully and avoided if possible to prevent further renal damage.

ACE inhibitors, angiotensine receptor blockers (ARBs), diuretics and aminoglycosides are the other nephrotoxic agents that affect renal functions adversely in myeloma patients and should be stopped or avoided if possible.

3.4 Hyperuricemia

Hyperuricemia due to increased nucleic acid turnover, is present in upto 50% myeloma patients at diagnosis. It may also be seen as a result of chemotherapy even though tumor lysis syndrome and acute uric acid nephropathy are rare in multiple myeloma. Adequate hydration, alkalinization of the urine and prophylactic use of allopurinol can overcome this complication significantly.

3.5 Hyperviscosity syndrome

Hyperviscosity syndrome is a group of symptoms results from increased blood viscosity due to the excessive amounts of circulating proteins and commonly occurs in association with paraprotein disorders, such as Waldenström macroglobulinemia (IgM) and rarely multiple myeloma (IgA,IgG3,kappa). It is classically manifested by spontaneous bleeding from mucous membranes due to impaired platelet function, neurologic and pulmonary symptoms as a result of ischemia in brain and lung tissue and visual defects related to rehinopathy. Although this syndrome rarely affects the kidneys permanently, it may also lead to acute renal failure occasionally. Plasmapheresis may be used to decrease viscosity

significantly and also exchange transfusions and hydration may be administered in the treatment strategy.

4. Therapy modalities for myeloma kidney

4.1 Plasmapheresis

Extracorporeal removal of nephrotoxic light chains from the blood seems to be a reasonable approach in cast nephropathy and plasma exchange has been widely used in clinical practice to decrease serum FLC concentrations. However, there is no convincing evidence about the benefit of plasmapheresis in acute renal failure in multiple myeloma and conflicting outcomes have been reported by many studies ((Zuchelli P,et al,1988, Clark WF,et al,2005, Leung N,et al,2008) .

Currently, plasmapheresis is indicated for patients with acute renal failure due to myeloma cast nephropathy to assist in the rapid removal of circulating excess FLCs and must be done together with dexamethasone-based regimens to limit production of new light chains. Renal biopsy is primarily needed to confirm tissue diagnosis but in emergency conditions presence of very high levels of FLCs in the serum or urine may prompt initiation of plasmapheresis. Standart regimen includes five to seven exchanges within seven or ten days and may be repeated if necessary.

4.2 Dialysis

Dialysis is an alternative approach to remove FLCs from circulation but it is generally insufficient for large amounts of light chains. Both hemodialysis and peritoneal dialysis may be administered in patients with acute or chronic renal failure, however, plasmapheresis is relatively more effective in the way of light chain reduction acutely.

Recently, newer protein permeable and larger pored hemodialysis membranes that remove the FLCs more efficiently has been developed and studies focused on these high- cut off (HCO) dialysers. It has been demonstrated that daily, extended hemodialysis using the Gambro HCO 1100 dialyzer which has an effective cut-off for <50 kd proteins, could remove continuously large quantities of FLC (Hutchinson CA,et al,2007). A following pilot study handled by same team in 2009 concluded that in dialysis-dependent acute renal failure secondary to cast nephropathy, patients who received uninterrupted chemotherapy and extended HCO-HD had sustained reductions in serum FLC levels and independent renal function recovered in 74 percent of patients. An interruption in chemotherapy was found to be associated with unfavorable outcomes and therefore it was hard to distinguish the benefits of chemotherapy and HCO dialysis separately.

The **EU**ropean trial of free **LI**ght chain removal by ex**TE**nded haemodialysis in cast nephropathy (EuLITE) is a very recent prospective, randomised controlled, multicenter clinical trial of HCO dialysis versus conventional dialysis in patients with with cast nephropathy, dialysis dependent acute renal failure and de novo multiple myeloma who all receive bortezomib, doxorubicin and dexamethasone as chemotherapy (Hutchinson CA,et al,2008). This study is ongoing and if it suggests that if efficacious, this therapy will offer clinicians new options in the management of these patients.

4.3 Anti-myeloma treatment

4.3.1 Conventional chemotherapy

Renal dysfunction in myeloma patients usually indicates high tumor burden and aggressive disease and it is important to initiate an early, effective therapy to provide a remission and renal reversal immediately. Alkylator-based conventional chemotherapy with Melphalan-Prednisone (MP) was usually reserved for patients who are ineligible for ASCT because of advanced age >70 and/or severe comorbidities (Rajkumar SV,Kyle RA,2005). MP regimen is also insufficient in renal function recovery and dose adjustment problems due to the renal elimination of melphalan limit the efficacy of therapy. In a study of Nordic Myeloma Study Group ,by the treatment with alkylating agents and standard dose steroids, reversal of renal failure was found in 58% of patients, whereas 40% of patients with a creatinine 2.3mg/dl achieved a normal renal function (Knudsen LM,et al,2000).

Combination chemotherapies like Vincristin+ Doxorubicin+ Dexamethasone (VAD),or Cyclophosphamide + Dexamethasone, or Dexamethasone alone are more preferable regimens by clinicians to achieve a rapid control of the disease. Dose modification is not needed in renal failure because of low renal excretion of mentioned agents. From a single instution study in 94 patients who had renal failure with myeloma, renal function recovery was observed in 26% of cases by conventional combination chemotherapy. Median survival for these patients was 28.3 months, compared with 3.8 months for those with irreversible renal failure ($P<0.001$). Furthermore, survival was not significantly different in patients with renal recovery vs those with normal renal function ($P=0.97$). Response rate to chemotherapy was found to be considerably lower in patients with renal failure than those with normal renal function (39% versus 56%; $P<0.001$). However, if patients dying within the first 2 months of treatment were excluded, there was no significant differences in the response rate between patients with renal failure and those with normal renal function. This result can be explained by high rate of early mortality in patients with renal failure accounting for 30% within first two months. Combination chemotherapy was also found to be more effective than MP or CP regimens with the response rates relatively 50% versus 24% ($P=0.03$) even though survivals were similar (Blade J,et al,1998).

4.3.2 High-dose dexamethasone-based regimens

High-dose dexamethasone-based regimens are alternatively safe and effective for newly diagnosed myeloma patients with renal impairment. In the first study of pulse dexamethasone therapy in previously untreated patients, the overall response rate was 43% similar to VAD and serious complications were considerably fewer, 4% versus 27% (Alexanian R,et al,1992). In a series of 41 myeloma patients with renal impairment treated with high-dose dexamethasone, rate of renal function recovery was found 73% which was higher than the reversal rate of standart dose steroid included alkylator-based regimens. This study concluded that high-dose dexamethasone was effective even in one-half of patients with negative prognostic factors in terms of reversal such as massive proteinuria, cast nephropathy and severe renal insufficiency. It is also suggested that combination with novel biologic agents, such as thalidomide and/or bortezomib also can provide a more rapid improvement in renal function (Kastritis E,et al,2007).

4.3.3 Novel agents

Overall survival in multiple myeloma has improved remarkably in the last decade with the introduction of three novel agents used in both denovo and relapsed MM; Thalidomide, Bortezomib and Lenalidomide (Kumar SK,et al,2008). Combination of bortezomib and high-dose dexamethasone is considered as the primary treatment option for myeloma patients with renal impairment and improves renal function rapidly in most patients. Incorporation of mechanical removal of serum FLCs may also provide an additive benefit to this combination for patients with acute renal failure due to myeloma cast nephropathy. Thalidomide is also therapeutic choice for the patients with severe renal impairment; however there is limited experience and data about it. Lenalidomide can reverse renal dysfunction in a subgroup of myeloma patients with mild or moderate renal impairment, thus it is effective and safe if administered at reduced doses according to renal function.

4.3.3.1 Thalidomide

Since the relationship between bone marrow angiogenesis and disease progression in myeloma has been well established, anti-angiogenic drug thalidomide has been demonstrated to be useful in the treatment of myeloma. Thalidomide is the first immunomodulatory drug (Imid) with proven anti-myeloma activity. No dose adjustment is required for the patients with renal impairment owing to the fact that it is not excreted in kidneys.

In a study of 20 patients with stage III relapsed or refractory myeloma and chronic renal failure, treatment with thalidomide alone or in combination with dexamethasone resulted in 12 of 15 responsive patients who recovered to normal renal function. Furthermore two patients who were dialysis-dependant showed a reduction in serum creatinine. Toxicity profile of thalidomide with or without dexamethasone was not significantly different among the patients with renal failure and normal renal function. Thus, it has concluded that thalidomide can be safely administered in patients with advanced myeloma and renal failure (Tosi P,et al,2004). In another study reversal of renal failure observed in 80% of previously untreated patients who received thalidomide in combination with high-dose dexamethasone with or without bortezomib (Kastritis E,et al,2007). Although many studies indicate similar toxicity in any level of renal dysfunction, some reports have suggested that toxic effects of thalidomide as severe neuropathy, constipation, lethargy and bradycardia are more frequent in patients with a serum creatinine level over 3mg/dl (Pineda-Roman M, Tricot G,2007). Treatment with thalidomide has been also reported in association with severe hyperkalemia in small part of patients with renal impairment (Harris E,et al,2003). More recently in a study of highcut off haemodialysis with thalidomide therapy, 14 of 19 patients recovered renal function and became independent of dialysis (Hutchison CA,et al,2009).

4.3.3.2 Lenalidomide

Lenalidomide is a small molecule analogue of thalidomide and a second generation immunomodulatory drug which is highly effective in patients with relapsed or refractory myeloma, especially in combination with dexamethasone or alkylator agents. It is mainly excreted in kidneys by both glomerular filtration and active tubular reabsorption and dose adjustment is required for the patients with renal impairment. Therefore, data on the

efficacy of lenalidomide in myeloma patients with severe renal failure is limited, because most of studies excluded patients with serum creatinine >2 mg/dl.

MM-009 and MM-010 phase 3 studies that compared Lenalidomid plus dexamethasone versus dexamethasone alone in patients with relaps or refractory myeloma demonstrated that there was no difference in disease response rates between patients with any degree of renal impairment and with normal renal function. In moderate or severe renal impairment, 72% of the patients had an improvement in their renal function with Len+Dex, although there was an increased incidence of thrombocytopenia in patients with creatinine clearance <50 ml/min (Dimopoulos MA,et al,2010). In the following study of same researchers, patients treated by Len+Dex at a dose adjusted according to renal function, 3 of 12 patients with renal impairment (25%) achieved complete renal response and 2 (16%) achieved minor renal response, moreover there were no differences in the incidence of adverse events among patients with and without renal dysfunction. A Spanish retrospective analysis reported that with the combination of Len+Dex, response rate was 57% in 15 dialysis-dependent myeloma patients ;one patient became independent of dialysis (Roig M,2009). In a phase II study which included treatment-naive patients who received Len+Dex showed that patients with a baseline Cr Cl< 40 ml/ min were 8.4 times more likely to require lenalidomide dose reduction due to grade 3 or higher myelosupression (Niesvizky R,et al,2007). Eventually available data suggest that lenalidomide may be safely administered to patients with renal impairment at the recommended reduced dose based on renal function with similar anti-myeloma activity and without significant additional toxicity. Recommended administration of lenalidomide is described as no dose reduction for CrCl<50 ml/min, reduce the dose to 10 mg/d in patients with CrCl 30-50 ml/min; to 15 mg every other day in patients with CrCl<30 ml/min not on dialysis and to 5 mg once daily in patients requiring dialysis.

4.3.3.3 Bortezomib

Bortezomib is the first proteasome inhibitor with proven activity in both newly diagnosed and relapsed or refractory myeloma. It may be used alone or in combination with steroids and other chemotherapeutic agents safely in patients with renal failure because its pharmacokinetics are independent of renal clearance and no dose adjustment is required.

In the SUMMIT (Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy) and CREST (Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma) phase 2 trials; overall response rates were found 45% in patients with CrCl>80 ml/min and 25% in those with CrCl<50 ml/min. Toxicity and discontinuation rates were similar between the patients with renal impairment and normal renal function (Jagannath S, et al, 2005). In APEX (Assessment of Proteasome Inhibition for Extending Remissions), a phase III study, bortezomib versus high-dose dexamethasone was assessed in terms of efficacy and safety in patients with relapsed myeloma with varying degrees of renal impairment. Time to progression (TTP) and overall survival (OS) were similar between the subgroups with CrCl>50 ml/min and <50 ml/min, although there was insignificant trend toward shorter TTP and OS in patients with CrCl 50 ml/min or below. OS was significantly shorter in dexamethasone-treated patients with any degree of renal

dysfunction (P=0.003), indicating that bortezomib is more effective than dexamethasone in overcoming the poor prognostic effect of renal failure. Toxicity of bortezomib was similar between subgroups (San Miguel JF,et al,2008).

In a retrospective analysis of 24 relapsed or refractory myeloma patients who were all dialysis-dependent, overall response rate was reported 75% with complete or near complete renal response (CR or nCR) rate of 30%. Three patients became dialysis-independent after bortezomib therapy and safety profile of bortezomib was found similar in any stage of renal impairment (Chanan-Khan AA,et al,2007). In a phase II study that assessed the efficacy of BDD (bortezomib + doxorubicin + dexamethasone) therapy in patients with multiple myeloma with light chain-induced acute renal failure, myeloma response and renal response were obtained in 72% and 62% of patients respectively. Survivals were not different between patients with and without renal response but was lower in previously treated patients (P <0 .001) (Ludwig H,et al,2009).

VISTA (Velcade as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone) is the largest analysis of a phase III trial comparing VMP (bortezomib+melphalan+prednisone) and MP (melphalan+prednisone) combinations in myeloma patients with renal impairment. Response rates were higher and TTP and OS longer with VMP versus MP across renal cohorts. Response rates in VMP arm and TTP in both arms did not appear significantly different between patients with CrCl ≤ 50 or >50 ml/min; OS appeared slightly longer in patients with normal renal function in both arms. Renal impairment reversal was seen in 49 of 111 (44%) patients receiving VMP versus 40 of 116 (34%) patients receiving MP. In both arms, rates of grade 3 and 4 adverse events appeared higher in patients with renal impairment; with VMP, rates of discontinuations or bortezomib dose reductions due to adverse effects did not appear affected (Dimopoulos MA,et al,2009).

According to the consensus statement on behalf of the International Myeloma Working Group, high dose dexamethasone and bortezomib are the recommended treatment for MM in patients with any degree of renal impairment especially for those with light chain cast nephropathy.

5. Light chain amyloidosis (Primary, AL amyloidosis)

Light-chain amyloidosis (AL) is the most common form of systemic amyloidosis in western countries, with an estimated incidence of 0.8 per 100,000 person years. This entity is characterized by tissue deposits of insoluble immunoglobulin light chain fragments which polymerize into extracellular amyloid fibrils with a typical β-pleated sheet secondary structure. Amyloid deposits derived from light chains accumulate in normal tissues like most commonly in the kidney, heart, liver and peripheral nervous system, resulting in structural organ dysfunction. It may be associated with an underlying plasma cell disorder like multiple myeloma, Waldenström Macroglobulinemia or MGUS (monoclonal gammopathy of undetermined significance). It is more commonly derived from the variable region of lambda light chain than kappa (75% vs. 25%) and rarely seen in association with heavy chains (AH-amyloidosis). Renal involvement is the most common manifestation in about 60–74% of cases and usually presents as nephrotic syndrome with progressive worsening of renal function (Kyle RA, Gertz MA,1995, Obici L,et al,2005). All compartments

of the kidney may be involved though predominant localisation is glomerulus. Renal failure at presentation is seen in 20% of patients generally observed with massive proteinuria and progresses to end-stage renal disease (ESRD) in ~40% of patients over a median time of 35 months (Bergesio F,et al,2008). In approximately 10% of patients, amyloid deposition occurs in the renal vasculature or tubulointerstitium rather than glomeruli, resulting in renal dysfunction without significant proteinuria.

5.1 Pathogenesis of AL amyloidosis

AL amyloid fibrils are derived from the N-terminal region of monoclonal immunoglobulin light chain which contains a variable (VL) domain. It is postulated that certain amino acid sequences for λ light chains change the thermodynamic stability and hydrophoby of the protein, leading to increased potential of fibril forming. It has been shown that λ VI light chains are more specifically associated with AL-amyloidosis (Solomon A,et al,1982). Furhermore posttranslational modifications of the light chains, such as glycosylation, may promote the amyloidogenic potential by protecting the fibril from degradation. β-pleated sheets are mainly responsible for the aggregation of light chains to form oligomers which do not dissolve in normal proteolysis and these aggregates are stabilized with other proteins, including glycosaminoglycans, proteoglycans, serum amyloid P (SAP), fibronectin and apolipoprotein E.

Mesangium is the initial site of the glomerular injury and amyloid fibrils replace the normal mesangial matrix by endocytosis of mesangial cells and transporting into lysosomes. Extracellular amyloid fibrils also stimulate the activation of matrix metalloproteinases (MMPs) and inhibit TGF- β as a regulator of matrix production, result in decreased synthesis of mesangial matrix. Tissue architecture is destroyed by amyloid deposits with its secondary effects on matrix and also direct toxicity, thus glomerular damage occurs which leads to renal failure.

5.2 Diagnosis of AL amyloidosis

AL amyloidosis is a rare disorder and it is difficult to diagnose because of nonspecific early clinic manifestations before specific organ failure occurs. Its diagnosis should be suspected in any patient with non-diabetic nephrotic syndrome, peripheral neuropathy, hypertrophic cardiomyopathy, hepatomegaly and macroglossia, especially when they are associated in a patient with typical age of >60 and male sex.

All amyloidosis-suspected patients need the diagnosis which is confirmed histologically. Abdominal subcutaneous fat aspiration is recommended as the initial minimal invasive diagnostic procedure and when it is combined with bone marrow biopsy, amyloid deposits may be identified in 90% of patients. If both examinations are negative, then a renal biopsy may be indicated and diagnostic in >95% of patients with manifest renal disease. Histopathological assessment characteristically contains congo red-positive staining leads to the apple-green birefringence under the polarized light microscopy. Amyloid deposits are always seen as diffuse amorphous hyaline material in glomeruli especially in mesangium and also in the wall of blood vessels. Electrophoresis with serum (71% sensitivity) and urine (84% sensitivity) immunofixation needs to be performed in all patients . after confirming the histopathologic diagnosis, to differentiate the type of amyloidosis Quantitative Ig

measurement, Ig-free light chain λ and κ testing, 24-hour urine total protein measurement (more than 0.5 g per day; mainly albumin), complete blood count, creatinine level, alkaline phosphatase level, measurement of troponin, brain natriuretic peptide, or N-terminal pro–brain natriuretic peptide levels, and echocardiography should be the following examinations for a complete diagnosis of AL amyloidosis.

5.3 Prognosis and treatment of AL amyloidosis

The survival of patients with amyloidosis is considerably variable, depending on some prognostic factors like the presence of coexisting myeloma, the number of organs involved especially the presence and severity of cardiac involvement, and response to therapy. Although the median survival is ranging from 12 to 18 months in different series, by the developments in treatment approaches, quality of life and survival have been considerably improved. In a retrospective analysis of 147 patients with AL amyloidosis, 20 patients had concurrent multiple myeloma and patients with both AL and myeloma had a significantly worse prognosis than those with AL alone with OS as 14 versus 32 months (Pardanani A,et al,2003). In a prospective study of 220 patients with primary systemic amyloidosis, the most important prognostic factor was reported as cardiac involvement and it was associated with the poorest prognosis with median survival less than 6 months. Nephrotic syndrome and renal failure were also poor prognostic factors with median survival rates of 15 and 16 months respectively, compared with 26 months in patients with normal renal function (P=0.007) (Kyle RA,et al,1997)

Standart cytotoxic chemotherapies have been widely used in last decades to inhibit the production of amyloidogenic light chains which usually include melphalan and prednisone or high dose dexamethasone. In a few small studies; combination of melphalan+prednisone achieved a reduction or complete resolution of proteinuria and improvement in renal function (Cohen J,et al,1975, Benson MD,1986). In a phase 2 study of 45 patients who were ineligible for ASCT, the combination of high-dose dexamethasone with melphalan was found more effective with a hematological response of 67% and functional organ improvement as 48% (Palladini G,et al,2004).

Although thalidomide is poorly tolerated by amyloidosis patients and treatment-related toxicity is frequent, with dose escalation, thalidomide+dexamethasone can be considered an option, alone or in combination with cyclophosphamide for the treatment of patients who relapse after melphalan-dexamethasone or ASCT. In a trial of 75 patients which compared the safety and efficacy of CTD in standart and attenuated doses, organ responses were found in 31% of the 48 hematologic responders, but no patient with ESRD became dialysis independent and no objective cardiac responses were observed. (Wechalekar AD,et al,2007) Lenalidomide also has been combined with dexamethasone in the treatment of AL amyloidosis and a phase 2 trial demonstrated that haematologic response rate was 67% and 41% of the patients with renal involvement experienced more than 50% reduction in urinary protein excretion without worsening of renal function (Sanchorawala V,et al,2007). Recent studies have suggested that bortezomib with or without dexamethasone is significantly active in AL amyloidosis and induces rapid responses and high rates of hematologic and organ responses. In a retrospective report which includes the AL patients who were treated or untreated previously, overall response rates were found 81% and 76% respectively, with bortezomib+dexamethasone combination (Kastritis E,et al,2010). In a case report of an AL

patient who have stage V renal disease with hemodialysis support and age above 65 years, relatvelygood response with acceptable tolerance has been shown with bortezomib+high-dose dexamethasone regimen (Mello RA,et al,2011).

In a selected patient group who are eligible for ASCT, by using a risk-adapted approach such as dose escalation of melphalan in patients with renal dysfunction, use of myeloablative chemotherapy followed by ASCT may be the most successful approach. In a study of 123 AL patients treated with high-dose melphalan followed by ASCT, renal response was noted in 43.4% of the patients with a better survival. It was also found that the severity of proteinuria was an independent predictor of renal response after ASCT and the recovery of renal function and prevention of ESRD after ASCT depended on the the degree of preexisting damage to the kidney (Leung N,et al,2007).

6. Monoclonal Immunoglobulin Deposition Disease (MIDD)

Nonamyloidotic monoclonal Ig deposition disease (MIDD) is characterized by deposition of monoclonal Ig subunits in kidney with an excess accumulation of extracellular matrix, leading to nodular sclerosing glomerulopathy, interstitial fibrosis, proteinuria, and renal insufficiency. According to the Ig deposition type, three subtypes of MIDD have been described, including light chain DD (LCDD), light-and heavy-chain (LHCDD) and heavy chain DD (HCDD). LCDD is the most prevalent subtype and found in 5% of patients with myeloma at autopsy series (Ivanyi B,1990). The most common cause is myeloma with the ratio of 65%, however 32% of cases are not associated with a manifested haematologic disorder. Although they are similar entities, in comparison to AL amyloidosis, the deposited light chains are kappa chains in 85% of LCDD cases, do not have a fibrillar organization and do not bind congo red. The majority of patients have a severe renal insufficiency with a median serum creatinine level of 3.8 mg/dl and usually tend to present with a higher serum creatinine concentration and lower rate of protein excretion than patients with AL amyloidosis (Harris AA,et al,1997). Cardiac, hepatic or small intestinal involvement also may be seen in MIDD.

6.1 Pathogenesis of MIDD

Initial process in MIDD usually includes the interaction between abnormal kappa chain (κ-I or κ-IV) and the mesangial cells of the glomerulus. Light chains were shown to stimulate the mesangial proliferation and secretion of transforming growth factor-beta (TGF-β) (Zhu L,et al,1995). TGF-β increases the production of collagen IV, laminin, and fibronectin which are deposited in the extracellular matrix (ECM) of the kidneys and also decrease the levels of collagenase, metalloproteinases, serin protease and other enzymes that degrades matrix proteins. Progressive light chain deposition and accumulation of ECM components inevitably lead to organ fibrosis and dysfunction. In MIDD, deposits predominantly localized in the tubular basement membranes and Bowman's capsule rather than in the glomeruli, though nodular glomerulosclerosis is present 60% of cases associated with a nephrotic range proteinuria. Tubular lesions are characterized by the deposition of a granular, punctuate, eosinophilic, periodic acid-Schiff (PAS)-positive, ribbon-like material along the interstitial side of the tubular basement membrane in electron microscopy. Glomerular lesions are usually associated with diffuse mesangial expansion by PAS positive

and Congo red negative nonfibrillar matrix that focally forms nodules. Deposits may also be seen in renal vasculature with same staining properties.

6.2 Diagnosis of MIDD

LCDD should be considered in the differential diagnosis of any patients with nephrotic syndrome and renal insufficiency of unknown origin. Standart testing procedure should be administered initially as in other plasma cell dyscrasias, and in most of the patients, elevated ratio of κ/λ free light chains in the serum and urine and a predominance of κ light chain–positive plasma cells on bone marrow biopsy help to confirm LCDD diagnosis. However, approximately 25% of patients have no demonstrable light chain in serum or urine by immunoelectrophoresis or immunofixation. A definitive diagnosis of LCDD is based on renal biopsy with elaborate histological examination and electron microscopy. Characteristic light microscopic, immunofluorescence, and electron microscopic findings which are mentioned before are the important keys for the diagnosis.

6.3 Prognosis and treatment of MIDD

The median survival of a patient with MIDD is 4 years, with survival at 1 yr and 8 yr of 66% and 31%, respectively. In largest studies, the variables that were independently associated with a worse patient survival were shown as age, initial creatinine, underlying multiple myeloma, and extrarenal LC deposition. Median time to progression to ESRD was reported to be 2.7 years and the 5-year uremia free survival was 37%. The only variables that were independently associated with renal survival were age and degree of renal insufficiency at presentation (Pozzi C,et al,2003). Renal and patient survivals were significantly worse in patients with LCDD who had coexisting cast nephropathy (Lin J,et al,2001).

Therapy of MIDD is similar to that for multiple myeloma and the main goal is to reduce Ig production in order to preserve renal function and improve survival. Combination of melphalan and prednisone has been used, but the response rates have been low with an 5 yr patient and renal survival of 70% and 37%, respectively. In patients with a serum creatinine < 4 mg/dl at presentation, stabilization or improvement in renal function after chemotherapy was found 60%, whereas 82% of patients with a serum creatinine >4 mg/dl progressed to ESRD despite therapy (Heilman RL,et al,1992). A combination of high-dose melphalan and autologous stem cell transplantation was reported to improve renal function without excessive morbidity or mortality. The largest study of ASCT in MIDD revealed that, serum creatinine improved by 50% or more in 4 of 11 patients and the nephrotic syndrome resolved in all, after ASCT (Royer B,et al,2004). In another study, patients who survived ASCT, high-dose chemotherapy and ASCT led to a median reduction in proteinuria of 92% and median improvement in GFR as 95% (Lorenz EC,et al,2008). Renal transplantation is associated with recurrence of LCDD in the transplanted kidney and effective chemotherapy or ASCT should be administered concurrently to control the underlying plasma cell dyscrasia. It is well established that bortezomib decreases TGF-β expression through inhibiting the NFκB pathway, thus recent researches focus on bortezomib-based chemotherapy in the treatment of MIDD and it appears to be safe and effective for the patients with renal dysfunction (Gharwan H, Truica CI,2011).

7. Renal tubular dysfunction

Multiple myeloma is the most common cause of proximal renal tubular acidosis in the adult. The toxic effect of light chains may be limited to tubular dysfunction and presented without renal insufficiency. This entity commonly occurs with kappa light chains. Some biochemical characteristics in the variable domain of the light chain has the capacity for resistance to protease degradation and a tendency to accumulate in tubule epithelial cells and form intracellular crystal formation. By the released intracellular lysosomal enzymes and the direct toxic effects of light chains, tubular damage occurs and clinic presentation includes the symptoms of Fanconi syndrome. Proximal renal tubular acidosis with loosing the potassium, phosphate, uric acid and bicarbonate resuting in aminoaciduria, renal glycosuria, hypophosphatemia, hyperchloremic metabolic acidosis, hypokalemia, proteinuria of tubular origin, and hypouricemia. Osteomalacia, chronic renal failure and chronic acidosis are the most common manifestations of Fanconi syndrome related to light chains. Episodes of dehydration may be seen due to polyuria and polydipsia. Furthermore, myeloma kidney may be aggravated with proximal dysfunction because of reduced light chain reabsorption and elevated precipitation in the distal nephron. With appropriate therapeutic management of underlying myeloma and vitamin D, calcium, and phosphorus supplementation for osteomalasic patients, considerable improvement can be obtained.

8. Conclusion

As we have tried to summarize above, kidney should be accepted one of the main targets in the course of myeloma especially in the diagnosis and treatment. Early diagnosis and prevention could result in preventing many renal complications and potential hazards during treatment period and if planned, stem cell transplantation.

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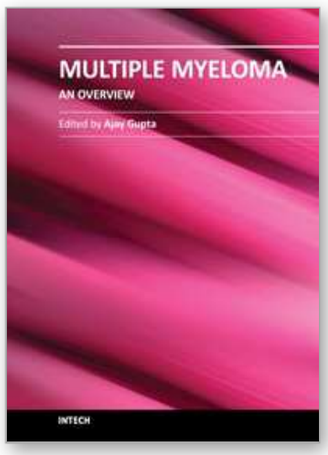

Multiple Myeloma - An Overview

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Multiple myeloma is a malignant disorder characterized by the proliferation of plasma cells. Much insight has been gained into the molecular pathways that lead to myeloma and indeed much more remains to be done. The understanding of these pathways is closely linked to their therapeutic implications and is stressed upon in the initial chapters. Recently, the introduction of newer agents such as bortezomib, lenalidomide, thalidomide, liposomal doxorubicin, etc. has led to a flurry of trials aimed at testing various combinations in order to improve survival. Higher response rates observed with these agents have led to their integration into induction therapies. The role of various new therapies vis a vis transplantation has also been examined. Recent advances in the management of plasmacytomas , renal dysfunction, dentistry as well as mobilization of stem cells in the context of myeloma have also found exclusive mention. Since brevity is the soul of wit our attempt has been to present before the reader a comprehensive yet brief text on this important subject.

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