Renal Complications in Multiple Myeloma and Related Disorders:
Survivorship Care Plan of the International Myeloma Foundation Nurse Leadership Board

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Kidney dysfunction is a common clinical feature of symptomatic multiple myeloma. Some degree of renal insufficiency or renal failure is present at diagnosis or will occur during the course of the disease and, if not reversed, will adversely affect overall survival and quality of life. Chronic insults to the kidneys from other illnesses, treatment, or multiple myeloma itself can further damage renal function and increase the risk for additional complications, such as anemia. Patients with multiple myeloma who have light chain (Bence Jones protein) proteinuria may experience renal failure or progress to end-stage renal disease (ESRD) and require dialysis because of light chain cast nephropathy. Kidney failure in patients with presumed multiple myeloma also may result from amyloidosis, light chain deposition disease, or acute tubular necrosis caused by nephrotoxic agents; therefore, identification of patients at risk for kidney damage is essential. The International Myeloma Foundation's Nurse Leadership Board has developed practice recommendations for screening renal function, identifying positive and negative contributing risk and environmental factors, selecting appropriate therapies and supportive care measures to decrease progression to ESRD, and enacting dialysis to reduce and manage renal complications in patients with multiple myeloma.

Renal dysfunction is one of the common clinical features of symptomatic multiple myeloma at presentation or throughout the course of the disease (Rajkumar & Dispenzieri, 2008; Rajkumar & Kyle, 2005). Studies have shown that the presence of renal failure indicates a higher tumor burden and, consequently, more aggressive disease (Dimopoulos, Kastritis, Rosinol, Blade, & Ludwig, 2008). Therefore, patients who are diagnosed with renal insufficiency should be treated aggressively because reversal of this condition results in survival outcomes similar to

At a Glance

✦ All patients with multiple myeloma have or are at risk for developing kidney dysfunction.

✦ Many inherent and acquired disorders can further place patients at risk for renal disease.

✦ Nurses should be aware of monitoring and assessments to preserve kidney function in patients with multiple myeloma.

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Digital Object Identifier: 10.1188/11.CJON.S1.66-76

those of patients who have normal renal function at diagnosis (Rajkumar & Kyle, 2005; Tariman & Faiman, 2011).

Patients may experience several types of renal failure. The National Kidney Foundation (NKF) clinical practice guidelines (NKF, 2010) define renal failure as serum creatinine levels of greater than 3 mg/dl. At least 20%–60% of patients will present with renal insufficiency or renal failure at some point in their disease (Blade et al., 1998; Tariman & Faiman, 2011), which in turn may negatively affect survival if not reversed. In addition, chronic insults to the kidneys (see Figure 1) from other illnesses, treatment, or the myeloma itself may have further negative impact on renal function.

The cost of care for patients with multiple myeloma is enormous (Cook, 2008; van Agthoven et al., 2004). Costs associated with patients in the United States who require dialysis are difficult to quantify. However, an in-house evaluation of patients requiring chronic dialysis at the Royal Preston Hospital in the United Kingdom was performed, and results indicated that treatment of patients with myeloma who have kidney dysfunction is 5%–33% more expensive than treatment of those patients without myeloma (Coward, 1989). The extra cost is attributed primarily to the greater number and longer duration of hospital admissions for infection (Coward, 1989).

Conditions that complicate the treatment of patients with multiple myeloma include older age at presentation; in older adult patients, renal clearance may be reduced by 35%–50% in the absence of renal disease as a normal aspect of aging (Dimopoulos, Alegre, et al., 2010). Other complicating factors include multiple coexisting morbidities, such as hypertension, diabetes, or other chronic health conditions (Rajkumar & Dispenzieri, 2008). Patients may experience renal failure or progress to end-stage renal disease (ESRD) and dialysis because of light chain cast nephropathy (i.e., damage to the kidneys as a result of the light chain paraprotein). Kidney failure in patients with a presumptive diagnosis of multiple myeloma also may be a result of damage similar to other disorders where a monoclonal paraprotein is secreted. These include light chain amyloidosis (AL), light chain deposition disease (LCDD), monoclonal immunoglobulin deposition disease (MIDD), or acute tubular necrosis (ATN) from the use of nephrotoxic agents in the setting of monoclonal gammopathy (Leung et al., 2008). Because renal disease in patients with multiple myeloma is heterogeneous, careful attention must be paid when selecting an appropriate treatment to decrease progression to ESRD and dialysis, which are associated with shortened overall survival (Blade et al., 1998; Blade & Rosinol, 2005).

Clinicians have the ability to identify patients at risk for kidney damage as a result of multiple myeloma and to institute preventive and therapeutic interventions; despite this, long-term negative effects still may result. The authors' goal is to describe the impact of and screening for kidney disease, examine contributing risk and environmental factors that may affect renal function, and provide recommendations to reduce and manage renal complications in patients with multiple myeloma. Adequate screening for acute or insidious development of kidney dysfunction is essential to these patients for early intervention to prevent long-term complications.

Clinical Presentations of Renal Insufficiency

Renal insufficiency is characterized by an elevated serum creatinine (normal range: 0.7–1.4 mg/dl). Other associated signs and symptoms include anemia, fatigue, fluid and electrolyte imbalances, and light chain proteinuria. In most studies, a serum creatinine concentration of 2 mg/dl or greater is used to define the presence of renal dysfunction in patients newly diagnosed with multiple myeloma (Rajkumar & Dispenzieri, 2008). Reduced glomerular filtration rate (GFR) of less than 60 ml per minute per 1.73 m^2 of body surface area calculated using the Modification of Diet in Renal Disease formula (Hallan, Asberg, Lindberg, & Johnsen, 2004) is indicative of renal dysfunction and is considered a clinically acceptable method of measurement (Dimopoulos, Terpos, et al., 2010; Kooman, 2009). Hydration status should be taken into account as temporary elevations in serum creatinine or decline in GFR may be seen in patients experiencing acute dehydration as a result of nausea and vomiting, infection, hypercalcemia, or nonsteroidal anti-inflammatory drugs (NSAIDs) (Knudsen, Hjorth, Hippe, & the Nordic Myeloma Study Group, 2000).

Clinical presentations largely depend on the pathogenesis of renal dysfunction. For example, nephrotic range proteinuria without significant renal impairment, orthostatic hypotension, and thickening of cardiac walls may indicate systemic AL (Rajkumar & Dispenzieri, 2008). Immunofixation showing a monoclonal protein is strong evidence of AL or LCDD in the presence of nephrotic syndrome (Gertz, 2002; Leung et al., 2008).

Since 2004, a nephelometric assay for serum free light chains (sFLC) has been used as a quantitative marker in the diagnosis and evaluation of patients with nonsecretory multiple myeloma (Dispenzieri et al., 2009). In patients with nonsecretory multiple myeloma, measurable amounts of monoclonal protein
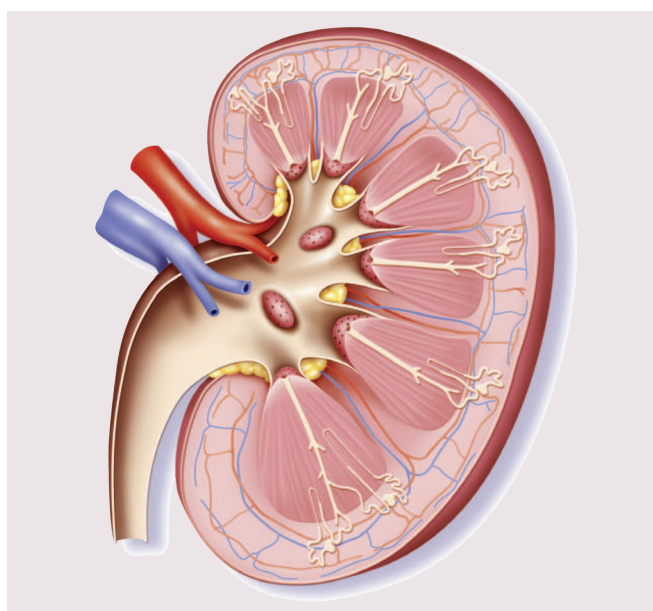

Figure 1. Cross Section of a Human Kidney

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are not secreted in the serum and/or urine, which provides a challenge for monitoring disease status. The sFLC assay relies on an imbalance between kappa and lambda light chains and is a surrogate marker for monoclonality (Bradwell et al., 2009; Dispenzieri et al., 2009). Several studies have evaluated the validity of the sFLC assay since its inception. One group was able to identify a light chain imbalance in 19 of 28 patients with nonsecretory myeloma (Drayson et al., 2001). In addition, abnormal sFLC ratios have been linked to a higher risk of progression from smoldering or asymptomatic myeloma to active multiple myeloma (Dispenzieri et al., 2008). A report by Kuhnemund et al. (2009) described 10 patients who appeared to have stable multiple myeloma as judged by conventional monitoring of intact immunoglobulin levels. However, when followed over a period of four years, these patients developed severe organ dysfunction as a consequence of initially undetected light chain progression, termed free light chain escape (Kuhnemund et al., 2009). Classic diagnostics, such as electrophoresis and quantitative immunoglobulin measurement, proved futile to detect light chain progression, whereas sFLC were reliable markers (Kuhnemund et al., 2009).

Light chain deposition disease is characterized by renal failure with nephrotic range proteinuria and usually kappa light chains. Lambda light chain proteinuria commonly is seen in AL (Rajkumar & Kyle, 2005). Fanconi syndrome is a disorder of proximal tubular transport, leading to urinary excretion of amino acids, glucose, bicarbonate, uric acid, phosphate, potassium, and low molecular weight proteins. The presence of hypophosphatemia, hypokalemia, hypouricemia, and glycosuria in a patient with normal serum glucose is strongly suggestive of Fanconi syndrome (Bridoux et al., 2005).

The Long-Term Effects of Multiple Myeloma on Renal Function

Unfortunately, by the time many patients have been diagnosed with multiple myeloma, mild to moderate kidney damage may have already occurred. Therefore, nurses must be aware of the pathogenesis of renal failure in myeloma, disorders similar to multiple myeloma, and monitoring strategies to employ to prevent further kidney damage.

Pathogenesis of Renal Insufficiency in Myeloma

Cast nephropathy is the most common cause of damage to the kidneys as a result of myeloma cell deposition, also called *myeloma kidney*. Protein casts appear on microscopic evaluation and essentially clog the kidney tubes. The casts are surrounded by multinucleated giant cells located in the distal and collecting tubules. These large, dense, tubular casts can precipitate in the tubules and obstruct and rupture the tubular epithelium. Tubulointerstitial damage may occur in the form of flattened tubular cells, degeneration with necrosis, and stripping away of the tubular basement membrane, leading to tubuloepithelial cell atrophy and interstitial fibrosis (Dimopoulos et al., 2008; Leung et al., 2008).

The glomerulus is responsible for filtering immunoglobulin light chains before the light chains are catabolized or excreted in the urine. Light chains present in the urine may overwhelm the proximal tubules' ability to catabolize the proteins. As proteins reach the nephrons, light chains may combine with Tamm-Horsfall mucoprotein, leading to cast formation (Dimopoulos et al., 2008). The process is manifested as large casts obstructing the tubules, which may lead to increased serum creatinine levels, decreased GFR, and increased risk for further deterioration of renal function (Gertz, 2005).

Acute Tubular Necrosis

ATN can be precipitated by dehydration in the presence of kappa or lambda light chains that may deposit in the kidney, as described earlier. The use of loop diuretics also may contribute to cast formation and increased serum creatinine levels. Vasoconstriction as a result of hypercalcemia and decreased blood flow from the kidneys as a result of the use of NSAIDs or aminoglycosides also may damage the kidneys (Tariman & Faiman, 2011).

Amyloidosis

AL is a disease characterized by the deposition of amyloid fibrils that consist of monoclonal light chains in various tissues of the body, often leading to organ dysfunction. Amyloid is a fibrillar structure that most commonly deposits in the heart, kidneys, nervous system, or gastrointestinal tract (Gertz, 2002).

Symptoms at presentation can be vague and depend on the affected organ, which often makes this disease difficult to diagnose. Clinical presentation may include nephrotic syndrome, congestive heart failure, peripheral neuropathy, macroglossia, periorbital purpura, or hepatomegaly (Gertz, 2002). If AL is suspected, a biopsy should be conducted to confirm the diagnosis. Subcutaneous fat (fat pad biopsy), rectal, renal, heart, or liver biopsy with positive Congo red staining confirms the diagnosis of AL (Haroun et al., 2003). In addition, a bone marrow aspirate and biopsy should be performed to demonstrate the presence of monoclonal plasma cells (Gertz, 2002).

In the kidney, amyloid deposits are predominantly found within the glomeruli (Dimopoulos et al., 2008). Patients usually present with significant proteinuria, but not always with renal failure. Progression to renal failure can be slow (Rajkumar & Dispenzieri, 2008).

Light Chain Deposition Disease

In LCDD, diagnosis is supported by immunofluorescence and electron microscopy. Linear peritubular deposits of monotypic light chains usually are found, but these deposits also are found along the basement membrane, mesangial nodules, Bowman's capsule, vascular structures, and in the interstitium (Dimopoulos et al., 2008). In addition to the glomerular findings, the presence of interstitial fibrosis is a frequent finding. The pathology of light chain deposition disease differs from amyloid; these deposits have a granular rather than fibrillar structure. LCDD usually consists of kappa light chains, which do not stain with Congo red (Herrera, Poblet, Cabrera, Pedrero, & Alonso, 2008), and the deposits are typically found in the renal tubular basement membranes (Gertz, 2005).

Clinical presentation includes nephrotic syndrome, anemia, and, eventually in almost all cases, renal failure. In LCDD, kidney

involvement is frequently part of a more diverse and complex clinicopathologic picture when compared with AL. Diagnosis of LCDD requires a renal biopsy (Dimopoulos et al., 2008). Both LCDD and renal AL have poor prognoses; however, newer therapies such as bortezomib and lenalidomide in combination with dexamethasone or prednisone have demonstrated efficacy in the treatment and maintenance setting. Autologous stem cell transplantation also may be considered in patients with AL or LCDD (Dimopoulos et al., 2008; Rajkumar & Dispenzieri, 2008).

Diagnosis of Renal Insufficiency

Renal insufficiency is evidenced by serum creatinine levels greater than 2 mg/dl; it may improve and even resolve in some patients if detected early and treated appropriately. Electrophoresis and immunofixation of serum and urine (an aliquot from a 24-hour urine collection) are necessary. Electrolytes and serum creatinine should be measured. Complete blood count (CBC) testing may identify anemia secondary to renal failure. Baseline and periodic monitoring of sFLC assays in patients with free light chain escape is important (Dispenzieri et al., 2008).

Impact of Kidney Dysfunction on Multiple Myeloma Therapeutics and Risk Factors

Elevated serum calcium levels (i.e., hypercalcemia) can lead to ATN and renal failure. Therefore, reversal of hypercalcemia with hydration, corticosteroids, and bisphosphonates is essential. Reducing tumor burden by initiating myeloma treatment, such as bortezomib with or without high-dose dexamethasone pulses, may be effective if renal insufficiency is related to myeloma (Rajkumar & Dispenzieri, 2008).

The efficacy of plasmapheresis in improving renal function has not been demonstrated conclusively in the few small-scale studies that have been conducted (Clark et al., 2005; Clark & Garg, 2008). Dialysis is indicated if the patient's GFR is critically low (estimated GFR 15 ml per min per 1.73 m² or below) and if symptomatic uremia is present (Hutchison et al., 2009). Extended hemodialysis using high-cutoff dialyzers may effectively remove sFLC and can lead to improved renal function (Hutchison et al., 2009).

Factors to Consider in Relapsed Myeloma

Despite therapy advancements made since the early 2000s that have increased survival rates, multiple myeloma remains incurable (National Comprehensive Cancer Network [NCCN], 2010b). A malignant clone eventually will re-emerge and relapse may occur along with renal insufficiency. As a result, nurses need to consider the safety of novel agents in patients with renal insufficiency. Agents such as bortezomib, thalidomide, and doxorubicin alone or in combination with steroids generally are well tolerated (Chanan-Khan et al., 2007, 2009). Lenalidomide can be given to patients with renal insufficiency or renal failure with dose modifications, as discussed later in this article. Other

agents such as cyclophosphamide and melphalan also generally are well tolerated by patients with renal insufficiency, but the dose of melphalan may be reduced based on the clinician's judgment (Celgene Corp., 2004).

Patients with myeloma often experience renal insufficiency because of disease progression. Although dexamethasone pulses may assist in reversing renal failure from hypercalcemia or disease progression, the overall benefit often is not sustained. Most practitioners will use bortezomib in combination with dexamethasone (Kastritis et al., 2007). The advent of novel treatments, using combination therapies to improve progression-free survival, offers options to treat patients at the time of relapse even in the setting of decreased renal function (NCCN, 2010b).

Additional Risk Factors

The NKF (2010) identified persons at increased risk for chronic renal disease, including those with diabetes, cardiovascular disease, hypertension, age greater than 60 years, racial or ethnic minority status in the United States, and those with a family history of chronic kidney disease. Patients with myeloma are at an increased risk of renal failure not only from their myeloma, but also from age and these other risk factors. Diabetes and hypertension are the leading causes of ESRD, with diabetes mellitus as the number one cause of kidney failure. About half of all new patients on dialysis have diabetes, making it the fastest growing risk factor for kidney disease. Blood pressure and blood sugar control can help prevent progression to ESRD (Firestone & Mold, 2009; O'Seaghdha et al., 2009). Common risk factors for kidney dysfunction in patients with myeloma are listed in Figure 2.

Hypertension is both a cause and a complication of chronic kidney disease and should be treated carefully and controlled in all patients. Penfield (2006) discussed how weight control, exercise, smoking cessation, and medications for controlling blood pressure may prevent or slow the progression to kidney failure in patients with multiple myeloma.

Because kidney function is reduced in older adults, the older the patient is, the greater he or she is at risk for developing renal insufficiency (Faiman, Bilotti, Mangan, Rogers, & the International Myeloma Foundation Nurse Leadership Board, 2008). Renal clearance may be reduced by a third to a half in older adult patients without other signs of renal disease, necessitating dose reductions for renally cleared drugs (Dimopoulos, Alegre, et al., 2010). In addition, patients with myeloma are at a higher risk for renal failure because of diabetes or steroid side

❑ Aminoglycoside antibiotics

❑ Comorbidities (e.g., diabetes, hypertension, increased age)

❑ Dehydration

❑ Hypercalcemia

❑ Nonsteroidal anti-inflammatory agents, including cyclooxygenase-2 inhibitors

❑ Progressive disease or cast nephropathy (particularly light chains)

❑ Radio-contrast dyes or IV contrast agents (e.g., for computed tomography scans)

Figure 2. Drugs or Conditions That May Contribute to Kidney Disease in Myeloma

effects and may require close monitoring and tighter control of their diabetes (Faiman et al., 2008). Some ethnic groups such as African Americans and Hispanics are at an increased risk for renal disease compared to Caucasians. All patients should be monitored for kidney disease, particularly in these groups.

Bone Complications

Bone loss associated with chronic renal disease is an osseous complication of multiple myeloma, and bone changes can begin in adults many years before symptoms appear. Older adult patients, postmenopausal women, and patients with multiple myeloma in general are at increased risk for osteoporosis, which progresses as renal function worsens (a result of renal osteodystrophy and hyperparathyroidism secondary to chronic renal disease) (Malluche, Koszewski, Monier-Faugere, Williams, & Mawad, 2006; Malluche, Mawad, & Monier-Faugere, 2010). Patients, in turn, experience increased risk of bone fractures and resultant joint and bone pain.

The kidneys play an important role in maintaining healthy bone mass throughout life by maintaining calcium and phosphorus levels in the blood. Normally, kidneys remove excess phosphorus from the blood. When the kidneys fail, though, serum phosphorus increases and combines with serum calcium, leading to lower circulating levels of calcium in the blood. The resultant hypocalcemia stimulates the parathyroid glands to release parathyroid hormone (PTH), which draws calcium from the bones to raise blood calcium levels. This results in osteopenia with weakening of the bones. Nurses should be aware that patients with chronic kidney disease (CKD) require routine monitoring for serum PTH and vitamin D (Levey et al., 2003). The International Myeloma Foundation's Nurse Leadership Board has addressed maintaining bone health as part of their survivorship care plan (Miceli et al., 2011).

Immunomodulatory Agents

Thalidomide and lenalidomide are immunomodulatory agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of myeloma. Dosage adjustments are not needed with thalidomide in patients with renal insufficiency (Celgene Corp., 2010b). Lenalidomide, in combination with dexamethasone, is FDA approved for the treatment of myeloma in patients who have received at least one prior therapy and its efficacy has been demonstrated in two pivotal phase III registration trials (Dimopoulos et al., 2007; Weber et al., 2007). Because lenalidomide is primarily excreted unchanged by the kidney, adjustments to the starting dose of lenalidomide are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis (Celgene Corp., 2010a). In a subanalysis of these trials, lenalidomide plus dexamethasone was demonstrated to lead to improvement in renal insufficiency in the majority of patients. With careful monitoring of creatinine clearance levels and appropriate dose adjustments, lenalidomide plus dexamethasone also is a highly effective and well-tolerated treatment for patients with myeloma who have renal insufficiency (Dimopoulos, Alegre, et al., 2010). Dose modifications for patients treated with lenalidomide based on renal insufficiency must be followed because renal insufficiency has been linked to increased myelosuppression

Table 1. Dose and Modification Guidelines for Lenalidomide in Patients With Renal Insufficiency

DEGREE OF RENAL IMPAIRMENT	RENAL FUNCTION (COCKCROFT-GAULT)	MODIFIED DOSE FOR MULTIPLE MYELOMA
Moderate	CLcr 30–60[a] ml per minute	10 mg every 24 hours
Severe (not requiring dialysis)	CLcr less than 30 ml per minute	15 mg every 48 hours
End-stage renal disease (requiring dialysis)	CLcr less than 30 ml per minute	5 mg once daily. On days of dialysis, the dose should be administered following dialysis.

[a] The definition of moderate renal impairment in the prescribing information approved by the European Medicines Agency for use in the European Union is $30 \leq CLcr < 50$ ml per minute.

CLcr—creatinine clearance

Note. The normal CLcr range for men is 97–137 ml per minute and 88–128 ml per minute for women.

Note. Based on information from Celgene Corp., 2010a.

(Dimopoulos, Alegre, et al., 2010) (see Table 1). In the absence of specific recommendations, CBC and chemistry panels should be monitored carefully in any patient with renal insufficiency who is receiving lenalidomide. Thalidomide requires no dose adjustments in renal insufficiency (Celgene Corp., 2010b).

Bortezomib is a proteasome inhibitor that is approved by the FDA for treatment of multiple myeloma with no dosage reductions for patients with renal failure (Millennium: The Takeda Oncology Company, 2010). A subset analysis of data from two key clinical trials in patients with relapsed myeloma demonstrated a response rate of 30% in patients with severe renal impairment (i.e., creatinine clearance of less than 30 ml per minute) and 25% in those with moderate renal impairment. In addition, patients with creatinine clearance values as low as 13.8 ml per minute have been included in clinical trials. The pharmacokinetics of bortezomib have been studied in patients with normal renal function and in patients with varying degrees of renal impairment from moderate to severe, including patients on dialysis (doses after dialysis). No differences were noted in bortezomib exposure among those with and without renal impairment (Millennium: The Takeda Oncology Company, 2010).

Chanan-Khan et al. (2007) conducted a multicenter retrospective study on the safety and efficacy of bortezomib in patients with multiple myeloma with renal failure requiring dialysis. The median serum creatinine level in the study was 6.8 mg/dl. Patients were treated with bortezomib alone or in combination with other agents (e.g., dexamethasone, liposomal doxorubicin, or thalidomide). The overall response rate was 75% among the 20 patients with response data. Three of four patients with impaired renal function had improved renal function following bortezomib-based therapy. That included one patient who was spared dialysis, and two patients who no longer required dialysis support after complete response. These findings suggest that bortezomib is a safe and useful agent in renal failure and dialysis-dependent patients (Chanan-Khan et al., 2007).

Newly Diagnosed Patients Eligible for Transplantation

Frontline therapy for the transplantation-eligible patient with decreased renal function includes regimens that contain thalidomide, dexamethasone, vincristine, doxorubicin, liposomal doxorubicin, cyclophosphamide, and bortezomib. Alkylating agents such as melphalan may be administered to patients who are not considered candidates for transplantation (NCCN, 2010b). The combinations of lenalidomide and dexamethasone (Rajkumar et al., 2010) or bortezomib and pegylated liposomal doxorubicin (Jakubowiak et al., 2009) have shown promising results in treating the myeloma. Clinical trials suggest that bortezomib with liposomal doxorubicin is a safe combination in the presence of renal insufficiency (Blade et al., 2008).

Autologous stem cell transplantation has been well documented as an effective treatment for patients with newly diagnosed myeloma as well as for those with relapsed or refractory disease (Attal et al., 1996, 2002, 2003, 2006, 2010; McCarthy, Owzar, Anderson, Hofmeister, & Hurd, 2010). However, few experts agree on the type of induction regimen, the use of single or tandem transplantation, and the role, if any, of allogeneic transplantation.

Transplantation may be considered in patients receiving dialysis, but morbidity and mortality are higher (Blade & Rosinol, 2005). In addition, the timing of transplantation, whether at diagnosis or relapse, is uncertain. Novel agents such as thalidomide, lenalidomide, and bortezomib should be considered for induction therapy.

Bortezomib is an effective treatment option for patients with renal insufficiency who are eligible for transplantation. In a phase II open-label intergroup trial, patients (N = 48) received a combination of bortezomib and dexamethasone prior to an autologous stem cell transplantation. The pretransplantation response rates included a complete response in 21% (n = 10) and 10% (n = 5) had very good partial remission (defined as more than 90% reduction of the M-component). Investigators concluded that the bortezomib plus dexamethasone regimen appeared effective and well tolerated in patients newly diagnosed with myeloma (Harousseau et al., 2006).

Newly Diagnosed Patients Not Eligible for Transplantation

Thalidomide and dexamethasone have been studied in older adult patients with myeloma. The use of high-dose dexamethasone

Patient Tear-Out Tool
Long-Term Survivor Renal Care Plan for Patients

Follow-Up Care for:	Recommendations:	Provider to Contact/Monitor:
Blood tests	A complete blood count, comprehensive metabolic panel, serum protein electrophoresis, serum immunofixation electrophoresis, 24-hour urine protein electrophoresis, urine immunofixation electrophoresis, lactate dehydrogenase, serum free light chain assay, and beta-2-microglobulin every three months. Special tests for bone loss may be ordered by the kidney specialist.	Treating hematology or oncology provider
Bone surveys	A metastatic skeletal survey annually or earlier if new skeletal symptoms occur.	Treating hematology or oncology provider
Diagnostic imaging	Avoid the use of IV dye or contrast with positron-emission and computed tomography or magnetic resonance image scans.	• Any provider may order one of these tests. • You, as the patient, should alert whoever is ordering these tests that you have a diagnosis of myeloma and IV dye may not be safe.
History and physical examination	Quarterly review of medications, changes in medical history, and physical examinations are recommended.	• Call your primary care provider for an annual physical examination. • Your hematology oncology practitioner will review medications at each visit.
Medications	• Avoid the use of nonsteroidal anti-inflammatory drugs such as ibuprofen. Many medications and over-the-counter supplements can worsen renal impairment, but others can be given safely with lower doses. • Bisphosphonates (zoledronic acid and pamidronate) often are used to prevent bone fractures and can be used with caution; your provider should check your kidney function before each dose. • Erythropoiesis–stimulating agents such as darbepoetin and erythropoietin are used to treat anemia; these must be used with caution, however, and a complete blood count must be obtained before each dose.	All medications should be reviewed with your provider before starting, including herbal and over-the-counter medications.
Nephrologist or kidney specialist follow-up	See nephrologist annually or as needed if change in creatinine is noted.	Nephrologist
Urinalysis	Check annually if not on pamidronate or zoledronic acid; check quarterly if you are receiving one of these drugs.	Treating hematology or oncology provider

Note. This patient education tool may be reproduced for noncommercial use.

is toxic for older adult patients and is not well tolerated (Palumbo & Rajkumar, 2009). Results of a clinical trial by San Miguel et al. (2008) reported that a combination of melphalan, prednisone, and bortezomib was superior to melphalan and prednisone (MP) in patients newly diagnosed with myeloma, including those with renal impairment. In the clinical trial, 682 patients were randomly assigned to receive either MP every six weeks or bortezomib plus MP on a six-week cycle with two three-week cycles of bortezomib and one cycle of MP. Bortezomib plus MP was superior to MP in time to progression, overall survival, complete response, progression-free survival, and time to next therapy.

The immunofixation-negative complete response rate was 35% for bortezomib plus MP compared with only 5% for MP, and a 52% reduction in risk of progression was noted for the group that received bortezomib plus MP. In the 185 patients with renal impairment (defined as creatinine clearance less than 60 ml per minute), no significant difference was noted in complete response rates, time to progression, or overall rate of survival compared with the 159 patients with normal renal function (defined as creatinine clearance of 60 ml per minute or higher). The data suggest that adding bortezomib to melphalan and prednisone is an effective upfront therapy for patients with multiple myeloma, including those with impaired renal function (San Miguel et al., 2008).

Supportive Care Recommendations

Bisphosphonates, such as zoledronic acid and pamidronate, are potent inhibitors of bone resorption that promote bone formation. However, bisphosphonates may be toxic to the kidneys in patients with renal insufficiency or chronic kidney disease (Miceli et al., 2011; Perazella & Markowitz, 2008). Pamidronate and zoledronic acid both are indicated for the purpose of decreasing skeletal-related events and fractures in patients with multiple myeloma, but their effects on patients differ. Pamidronate is less nephrotoxic but more likely to cause tubular injury and nephrotic syndrome (Kunin, Kopolovic, Avigdor, & Holtzman, 2004; Markowitz, Fine, & D'Agati, 2002; Perazella & Markowitz, 2008). That generally is seen with very prolonged use and/or higher doses. Zoledronic acid is more nephrotoxic than pamidronate, particularly in patients with uncontrolled myeloma, and is associated with toxic ATN (Kunin et al., 2004; Markowitz et al., 2002; Perazella & Markowitz, 2008). Clinicians need to be particularly careful with baseline elevation in serum creatinine because zoledronic acid can induce renal failure that may not be reversible (Perazella & Markowitz, 2008).

Caution must be exercised when using these drugs, which are FDA approved for patients with hypercalcemia of malignancy (pamidronate) and multiple myeloma (pamidronate and zoledronic acid) (Kyle et al., 2007). When renal function has stabilized, serum creatinine levels should be evaluated at baseline and prior to each infusion of bisphosphonates. Dose reductions of zoledronic acid and pamidronate also may be needed, and longer infusion times of pamidronate currently are recommended for patients with reduced creatinine clearance. Patients who are receiving bisphosphonates

also should be given 1,000 mg per day of calcium and 400 IU per day of vitamin D. However, calcium supplementation is contraindicated in patients with hypercalcemia (Faiman et al., 2008).

Anemia, defined in myeloma as a hemoglobin concentration 2 g/dl below the institutional limits of normal, is present in patients with moderate to severe renal dysfunction, but also may
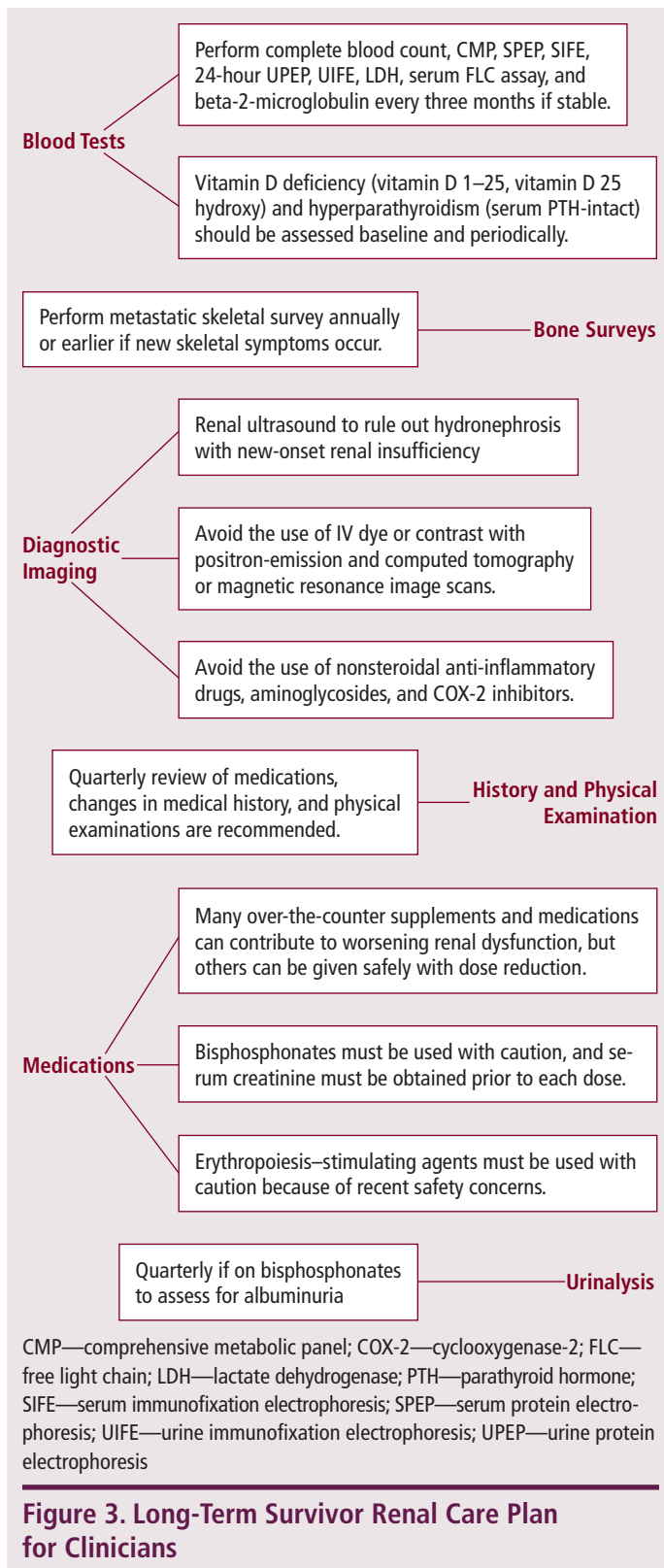
Blood Tests
- Perform complete blood count, CMP, SPEP, SIFE, 24-hour UPEP, UIFE, LDH, serum FLC assay, and beta-2-microglobulin every three months if stable.
- Vitamin D deficiency (vitamin D 1–25, vitamin D 25 hydroxy) and hyperparathyroidism (serum PTH-intact) should be assessed baseline and periodically.

Bone Surveys
- Perform metastatic skeletal survey annually or earlier if new skeletal symptoms occur.

Diagnostic Imaging
- Renal ultrasound to rule out hydronephrosis with new-onset renal insufficiency
- Avoid the use of IV dye or contrast with positron-emission and computed tomography or magnetic resonance image scans.
- Avoid the use of nonsteroidal anti-inflammatory drugs, aminoglycosides, and COX-2 inhibitors.

History and Physical Examination
- Quarterly review of medications, changes in medical history, and physical examinations are recommended.

Medications
- Many over-the-counter supplements and medications can contribute to worsening renal dysfunction, but others can be given safely with dose reduction.
- Bisphosphonates must be used with caution, and serum creatinine must be obtained prior to each dose.
- Erythropoiesis–stimulating agents must be used with caution because of recent safety concerns.

Urinalysis
- Quarterly if on bisphosphonates to assess for albuminuria

CMP—comprehensive metabolic panel; COX-2—cyclooxygenase-2; FLC—free light chain; LDH—lactate dehydrogenase; PTH—parathyroid hormone; SIFE—serum immunofixation electrophoresis; SPEP—serum protein electrophoresis; UIFE—urine immunofixation electrophoresis; UPEP—urine protein electrophoresis

Figure 3. Long-Term Survivor Renal Care Plan for Clinicians

be caused by blood loss, cytotoxic therapy, or increased disease activity. If blood loss is not found, and the anemia is not considered to be related to treatment or disease progression, assessing serum erythropoietin, iron, folic acid, and vitamin B_{12} levels may identify the type of anemia. Erythropoiesis–stimulating agents (ESAs) (i.e., erythropoietins such as epoetin alfa or darbepoetin alfa) may be used to manage anemia (NCCN, 2010a).

The use of ESAs in renal disease is accepted; however, their use in myeloma remains controversial. In addition, increasing concerns about ESA use abound, as multiple studies show decreased survival in patients with CKD and other cancers (Tariman & Faiman, 2011). The NCCN practice guidelines currently recommend that darbepoetin can be initiated at a dose of 2.25 mcg/kg^2 weekly, and 500 mcg every three weeks is an appropriate fixed dose (NCCN, 2010a). In addition, epoetin alfa can be given at a dose of 150 units three times weekly or up to 40,000 units weekly, subcutaneously. Long-term erythropoietin therapy may be associated with a functional iron deficiency; therefore, serum iron, ferritin, and serum total iron binding capacity should be assessed prior to initiating oral iron therapy.

Results of a study by Katodritou et al. (2008) suggested that ESAs may have a negative effect on the survival of patients with myeloma. In the study, 323 Greek patients with multiple myeloma were evaluated from 1988–2007. The median survival was 31 months for patients who received ESAs, compared with 67 months for those who were not exposed to ESAs. The median progression-free survival for patients in the ESA group was 14 months versus 30 months for those without ESA exposure (Katodritou et al., 2008).

Although these results suggest that using ESAs could lead to disease progression, the use of these drugs is recommended in NCCN guidelines for management of anemia (NCCN, 2010a). Because of the increased risk for thrombus, particularly in patients with multiple myeloma who are treated with ESAs, and the potential of decreased survival, the NCCN (2010a) recommends that the severity of anemia be assessed and the risks of ESA therapy versus blood transfusion be balanced with the benefits of therapy. Some clinicians, however, have called for re-evaluation of the use of ESAs in patients with cancer (Unger, Thompson, Blank, & Temple, 2010).

Supportive care considerations in the dialysis-dependent patient differ from those of the nondialysis-dependent patient with chronic renal insufficiency. Individuals undergoing dialysis can benefit from many of the available novel treatment strategies, but doses of bortezomib, thalidomide, and lenalidomide should be given after dialysis. Dose reductions for bortezomib are not required (Millennium: The Takeda Oncology Company, 2010), but modifications for patients receiving lenalidomide must be followed (Celgene Corp., 2010a).

Monitoring

Nurses and clinicians must closely monitor patients' myeloma and renal insufficiency by blood chemistry and CBC testing (see Figure 3). Additional assessment of myeloma parameters, such as serum and urine protein electrophoresis, serum beta-2 microglobulin, 24-hour urine for protein

electrophoresis, and sFLC assay also is necessary. Although the frequency of testing depends on the degree of renal failure as well as patients' response to therapy, testing CBC and chemistry laboratory parameters on a monthly basis is reasonable. The nurse may use the Chronic Kidney Disease Staging System outlined in Table 2 to monitor patients with renal dysfunction.

Special Considerations in Patients With Multiple Myeloma on Dialysis

About 20% of patients with multiple myeloma currently are receiving dialysis (Blade & Rosinol, 2005). Clinicians must be cognizant of the following potential issues and concerns surrounding patients requiring hemodialysis (Blade & Rosinol, 2005; Cook, 2008; Finkelstein, Wuerth, & Finkelstein, 2009; Penfield, 2006).

- **Finances:** Dialysis and supportive care associated with end-stage renal disease add to the cumulative costs of treating patients with multiple myeloma. That includes additional expenses when plasma exchanges are used to restore normal renal function.
- **Quality of life:** No study has examined the quality of life (QOL) of patients with myeloma on dialysis; however, research findings from QOL studies in chronic renal disease consistently have shown that patients' overall health-related QOL is compromised (Finkelstein et al., 2009).
- **Stem cell transplantation:** Cases of toxic deaths were no different between patients with low and normal GFRs, although patients with low GFR had more morbidity from mucositis, diarrhea, and infections (Blade & Rosinol, 2005; Finkelstein et al., 2009).
- **Renal transplantation in the setting of multiple myeloma:** Although renal transplantation generally is not considered for patients with multiple myeloma, it has been performed and could be considered for patients with ESRD whose myeloma is in remission (Taheri et al., 2007).

Table 2. Chronic Kidney Disease Staging System for Patients With Renal Disease (Stage I–IV)

STAGE	DESCRIPTION	KIDNEY FUNCTION[a]
I	Kidney damage with normal or increasing GFR	90 or higher
II	Kidney damage with mild decreasing GFR	60–89
T	**For transplant**	
III	Moderate decreasing GFR	30–59
IV	Severe decreasing GFR	15–29
V	Kidney failure	Less than 15
D	**For dialysis**	(or dialysis)

[a] GFR ml per minute per 1.73 m^2

GFR—glomerular filtration rate

Note. T for transplant represents all kidney transplant recipients; D for dialysis is at stage V for people being treated with dialysis.

Note. From "About Chronic Kidney Disease," by the National Kidney Foundation, 2011. Retrieved from http://www.kidney.org/professionals/KLS/aboutCKD.cfm. Copyright 2011 by the National Kidney Foundation. Reprinted with permission.

Conclusion

Renal insufficiency in patients with myeloma should be assessed at initial diagnosis and regularly throughout therapy. Preventive measures should be initiated at diagnosis and throughout the course of the disease. Nurses have the unique ability to play a key role in early identification of renal insufficiency and to provide patient education on preventive interventions such as liberal oral hydration and avoiding NSAID therapy (Brater, 1999). In addition, by ensuring that patients undergo routine laboratory evaluation with attention to serum calcium and creatinine levels, nurses may help patients avoid acute renal failure. Prompt intervention with hydration and identification of the underlying cause of renal failure may allow a patient's renal function to improve, provide patients with more therapeutic options, and offer the potential for increased survival and improved QOL.

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