MULTIDISCIPLINARY TEAM PRESENTATIONS BY

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LETTER TO OUR READERS

Dear Colleague:

It is my distinct pleasure to offer this newsletter entitled “Considerations in Multiple Myeloma: Renal Dysfunction.” In fact, over the next 7 months, we will publish 4 additional newsletters in this series featuring topics relevant to your multidisciplinary team approach to caring for patients with multiple myeloma (MM).

Together with a faculty of hematologists/oncologists, oncology nurses, and oncology pharmacists, we will focus our discussion on one topic for each newsletter. This premier issue focuses on patients with renal dysfunction. Upcoming topics include: hard-to-treat patients, treatment-naive patients, health economics, and side effect management.

It is our sincere hope that the information presented here is of value to you in your care of patients with MM.

Sincerely,

Sagar Lonial, MD
Associate Professor of Hematology and Oncology
Emory University

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Target Audience
This educational publication is designed for physicians, nurses, and pharmacists who wish to enhance their knowledge concerning the management of patients with multiple myeloma and renal dysfunction.

Learning Objectives
At the completion of this educational activity, you should be able to:
• Describe the prevalence of renal insufficiency among patients with multiple myeloma (MM)
• Recognize the special challenges in pharmacologic treatment of the many patients with MM who also have renal insufficiency, especially those requiring dialysis
• Discuss the results of studies showing treatments that are active and safe in MM patients with renal impairment, including those with advanced renal failure requiring dialysis

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Estimated Time to Complete This Activity:
1 hour

Date of original release: May 7, 2008
Valid for CME credit through: May 7, 2009
LETTER TO OUR READERS
Sagar Lonial, MD

CME INFORMATION

SYMPTOM MANAGEMENT IN MULTIPLE MYELOMA: RENAL INSUFFICIENCIES

SELECTED HIGHLIGHTS FROM THE 2007 ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY

CASE STUDY AND IMPLICATIONS FOR PHYSICIANS
Johnathan Kaufman, MD

Mission Statement
Multidisciplinary Cancer Care newsletters provide a forum for sharing expert interdisciplinary treatment perspectives on patient care with the ultimate goal of promoting ongoing professional education to physicians, nurses, and pharmacists in the hematology/oncology community.

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Renal impairment represents one of the major complications of multiple myeloma (MM). Depending on the definition of renal failure, this complication occurs in 20% to 50% of newly diagnosed patients. Up to 50% of patients newly diagnosed with MM have a decrease in creatinine clearance, and approximately 30% of patients have a serum creatinine equal to or higher than 1.5 mg/dL at the time of diagnosis. Studies have shown that the severity of renal impairment significantly affects the prognosis of patients with MM, and renal dysfunction has been associated with shorter survival. Therefore, careful monitoring for signs of renal insufficiency is important in MM patients. In addition, supportive care measures, such as hydration, and correction of hypercalcemia with bisphosphonate may be beneficial. As many as 13% of patients with MM require dialysis because of severe renal impairment. At the 2007 Annual Meeting of the American Society of Hematology (ASH) in Atlanta, GA, Hutchison and colleagues reported that 10% of MM patients require dialysis support, and of these, 80% remain dialysis dependent. At the present time, no standard guidelines have been established to treat MM patients with renal failure requiring dialysis.

Treatment regimens for MM have advanced slowly over the past 40 years, and relatively few effective treatment options exist for patients with MM. Traditional treatments include combination chemotherapy with melphalan/prednisone and vincristine/doxorubicin/dexamethasone (VAD). In the 1980s, a significant breakthrough occurred with the introduction of myeloablation with autologous stem cell transplantation (ASCT), which was proven to be an effective initial treatment for patients with newly diagnosed MM. Myeloablation with high-dose chemotherapy and subsequent rescue with ASCT has become a mainstay for patients fit enough to withstand the regimen, usually patients younger than 65 years of age. However, treatment options such as melphalan-based chemotherapy and high-dose chemotherapy with ASCT have limitations in MM patients with renal failure because of suboptimal survival benefits, excessive toxicities, early mortality, and/or the need for dose reductions and treatment discontinuations.

Since their introduction in the 1990s, the immunomodulatory agents thalidomide and lenalidomide have shown efficacy, alone or in combination with dexamethasone, in the overall population of MM patients. Thalidomide is considered safe in renal insufficiency and no dosage adjustment is needed for renally impaired patients on dialysis. Lenalidomide is substantially excreted by the kidney, so careful dose adjustment and observation of the complete blood count (CBC) should be instituted in order to minimize the potential for hematologic toxicity.

The most recent development in the treatment of MM is the introduction of bortezomib, a specific, reversible proteasome inhibitor indicated for the treatment of patients with MM who have received at least one prior therapy. Alone or in combination, bortezomib has been shown to be active and safe in MM patients with various degrees of renal impairment, including patients with advanced renal failure requiring dialysis, in the following studies:
- A subgroup analysis of 256 pa...

![Figure. Overall response rates by level of renal impairment.](image-url)
tients with recurrent and/or refractory MM from the phase 2 SUMMIT\(^\text{12}\) and CREST\(^\text{13}\) trials

- A retrospective analysis\(^\text{8}\) in 24 MM patients with advanced renal failure requiring dialysis
- A prospective National Cancer Institute (NCI) dose-escalating and pharmacologic study\(^\text{14}\) in adult cancer patients with impaired renal function

**Bortezomib in Patients With Impaired Renal Function**

A retrospective analysis of 256 patients enrolled in 2 phase 2 trials, CREST and SUMMIT, showed that single-agent treatment with bortezomib was effective in patients with all levels of renal impairment. Renal function did not appear to have a major impact on response rates, toxicity, or the ability to complete the protocol-specified 8 treatment cycles of 1.0 or 1.3 mg/m\(^2\) bortezomib on days 1, 4, 8, and 11 of 21-day cycles. Overall response rates—complete response (CR) + partial response (PR) + minimal response (MR)—were 45%, 33%, and 25% for patients with a baseline creatinine clearance (CrCl) >80 mL/min, 51 to 80 mL/min, and ≤50 mL/min, respectively (Figure).\(^\text{11}\)

In 10 patients with severe renal impairment (CrCl 13.8-30 mL/min), a response was seen in 3 patients (30%) (2 PR and 1 MR). Notably, 7 of the 10 patients completed the protocol-specified 8 cycles, and 2 patients continued therapy beyond 8 cycles in the extension trial.\(^\text{12}\)

Patients with CrCl >80 mL/min (n=105), 51 to 80 mL/min (n=99), and ≤50 mL/min (n=52) had similar rates of discontinuation and similar adverse event profiles. Dyspnea was the only adverse event reported significantly more frequently (12% vs 1%, P=0.01) in patients with a CrCl ≤50 mL/min compared to those with a CrCl >80 mL/min.\(^\text{10}\)

**Bortezomib in Patients With Renal Failure Requiring Dialysis**

In a multicenter retrospective case analysis by Chanan-Khan and colleagues, the feasibility and activity of bortezomib-based therapy was evaluated in MM patients (n=24) requiring dialysis support for advanced renal failure. Patients received bortezomib alone or bortezomib-based combination therapy. All patients were scheduled to commence dialysis at the time of bortezomib administration. However, 1 patient rapidly responded to bortezomib therapy and no longer required dialysis support.\(^\text{9}\)

Among 20 patients with available response data, overall response rate (CR + PR) was 75%, with 30% CR + near CR. One patient was spared dialysis, and 3 other patients became independent of dialysis following bortezomib-based treatment. These encouraging results suggest that bortezomib or bortezomib-based regimens can be used in MM patients requiring dialysis, with manageable toxicities.\(^\text{8}\)

Eighty-three percent of patients received bortezomib at a dose of 1.3 mg/m\(^2\) given in combination with other agents such as dexamethasone, thalidomide, and doxorubicin. Patients received a median of 5 cycles (mean, 7 cycles) of bortezomib treatment.\(^\text{9}\)

Most adverse events were graded mild to moderate and were manageable. As expected for bortezomib-based therapy, the most common adverse event was reversible thrombocytopenia (39%), with no bleeding events.\(^\text{8}\)

**Prospective Study of Bortezomib in Adult Cancer Patients With Impaired Renal Function**

At the 2007 Annual Meeting of ASH in Atlanta, GA, Mulkerin and colleagues presented the results of the first prospective study of the effect of renal impairment, including dialysis dependence, on bortezomib dosing and tolerability.\(^\text{11}\)

Bortezomib at doses of up to 1.3 mg/m\(^2\) on the standard schedule was well tolerated in patients with advanced malignancies and impaired renal function, including those requiring dialysis. In the majority of patients, bortezomib was administered following dialysis. The authors concluded that bortezomib clearance is independent of renal function and that bortezomib is a viable treatment option regardless of degree of renal impairment, including dialysis dependence.\(^\text{11}\)

Based on the findings of this NCI study, the US Food and Drug Administration (FDA) recently approved updated prescribing information for bortezomib. The pharmacokinetics of bortezomib is not influenced by the degree of renal impairment. Therefore, dosing adjustments are not necessary for patients with renal insufficiency. Since dialysis may reduce bortezomib concentrations, the drug should be administered after the dialysis procedure.\(^\text{14}\)

**References**


*Continued on page 8*
Selected Highlights From the 2007 Annual Meeting of the American Society of Hematology

Fu et al reported on a study (N=74) of MM patients in Tianjin, China, in which 56.8% of patients had renal dysfunction. The investigators found that patients with renal impairment had significantly shorter overall survival times than those without renal dysfunction (28 ±5 months vs 42 ±6 months), that hypertension and high tumor burden were risk factors for renal dysfunction, and that effective chemotherapy and support therapy helped restore renal function.

Treatment With Bortezomib-Based Regimens

Ailawadhi et al reported on a study (N=66) that evaluated whether varying degrees of renal dysfunction adversely affect the clinical outcome of bortezomib-based therapies. The number of patients with renal function stages (evaluated according to the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) of 1, 2, 3, 4, and 5 were: 9 (13.6%), 29 (44%), 22 (33.4%), 3 (4.5%) and 3 (4.5%), respectively (Figure 1). After treatment, complete response (CR) was observed in 8 patients (12%), partial response (PR) in 25 patients (38%), stable disease (SD) in 27 patients (41%), and progressive disease (PD) in 6 patients (9%) (Figure 2). There was no significant association between renal function and multiple myeloma (MM) stage (P=0.1722), Ig type (P=0.5288), untreated vs relapsed/refractory disease (P=0.1352), or response to treatment (P=0.5292). The study authors concluded that patients treated with bortezomib-based therapies experienced similar clinical benefit irrespective of their NKF K/DOQI renal function stage.

Roussou et al reported on a study that assessed the frequency of renal failure improvement and kinetics of serum creatinine in 20 patients who received bortezomib-based regimens. Patients had either newly diagnosed (n=7) or relapsed or refractory (n=13) MM and renal failure, defined as a serum creatinine ≥2 mg/dL. All patients received bortezomib plus dexamethasone alone or in combination with other agents, such as thalidomide, doxorubicin, or melphalan.

Reversal of renal failure, defined as a sustained decrease of serum creatinine to <1.5 mg/dL, was documented in 35% of all patients, with a median time to reversal of 23 days. Nine patients (45%) had a 50% decrease in serum creatinine, with a median time to the decrease of 34 days. Some decrease of creatinine was documented in 88% of patients. Among 4 patients who were on renal dialysis, 2 became independent of this procedure after the second and the third cycle of treatment. The objective response rate was 61%, and the median progression-free survival for responders was 12 months. Toxicities were similar to those seen in MM patients without renal failure who were treated with bortezomib-based regimens. Grade 3-4 neutropenia and thrombocytopenia were seen in 28% and 22% of patients, respectively. One patient died of infection, and bortezomib had to be discontinued in 4 patients due to grade 3 neurotoxicity.

The study authors concluded that bortezomib-based regimens administered to MM patients with renal impairment exhibit toxicity and efficacy similar to those observed in patients with normal renal function. They also concluded that these regimens are associated with rapid improvement of renal function in most patients and reversal of renal failure in one-third of them.

Ludwig et al reported preliminary data from 37 patients in an ongoing phase 2 study in MM patients with acute renal failure using the bortezomib-doxorubicin-dexamethasone regimen. The overall response rate in the 22 evaluable patients was 73%, with 12 patients (54%) achieving CR/nCR. Acute renal failure could be reversed in 9 patients (41% of the total, or 56% of patients with CR-PR). After dose reduction of the initial regimen, treatment was well tolerated in this high-risk patient population.

Autologous Stem Cell Transplantation (ASCT)

Chodirker et al presented a retrospective review of 22 MM patients who were receiving dialysis support at the time of ASCT. Partial responses were achieved in 18 out of 22 patients. Progression-free survival from the time of transplant was 22.3 months. Three patients (13%) became dialysis-independent (all within 30 days posttransplant). At a median follow-up of 29.6 months (range 0.8-79.6), 10 out of 22 patients (45%) were alive. The estimated median overall survival time from the date of transplant was 60 months, with a 5-year survival probability of 53.2%.

The study authors concluded that ASCT in dialysis-dependent MM patients results in response rates and survival data comparable to those in nondialysis populations. However, it carries increased toxicity, prolonged median days to discharge (19 days vs institutional mean of 14 days) and a higher treatment-related mortality (13.6% vs institutional mean of 1.6%). The authors observed that the higher rates of cardiac and neurological toxicities enforce the need for pretransplant identification of patients with comorbidities, and that dose reduction and risk factor optimization should be considered in these patients.
Parikh et al reported on the outcome in 48 patients who received ASCT for MM while in renal failure, defined as serum creatinine ≥2 mg/dL sustained for >1 month. Nine of the patients (19%) were dialysis dependent. Nine patients (19%) achieved a complete response, with a total response seen in 32 patients (67%). Two patients (4%) died within 100 days of the autotransplant. Grade ≥1 mucositis was seen in 21 patients (43%), with 3 patients (6%) experiencing grade ≥3 mucositis. After a median follow up of 34 months, the estimated median progression-free survival (PFS) and overall survival (OS) were 21 and 87 months, respectively. Kaplan-Meier estimates of 5-year PFS and OS probabilities were 21% and 54%, respectively. Significant improvement in renal function, defined as an increase in glomerular filtration rate of 25% above baseline by 1 year post-transplant, was seen in 17 patients (35%). None of the 9 dialysis-dependent patients became dialysis independent. A pretransplant creatinine level of ≥3 mg/dL was associated with a significantly shorter overall survival (P=0.05), but did not adversely impact the improvement in renal function (P=0.6).

The authors conclude that ASCT after high-dose therapy is safe and feasible in patients with MM and renal failure. Response rates and outcomes were similar to those observed in other patients. Approximately 35% of patients had a significant improvement in renal function after transplant.

References

5. Chodirker L, Nikhail, JR, Stewart K, et al. Autologous stem cell transplantation (ASCT) is multiple myeloma (MM) patients with dialysis-dependent renal failure is effective but carries high rates of toxicity. Presented at the 49th Annual Meeting of the American Society of Hematology; December 8-11, 2007; Atlanta, GA. Abstract 954.

Renal Insufficiencies

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CASE STUDY AND IMPLICATIONS FOR PHYSICIANS

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A 58-year-old man was in his usual state of good health when he presented to his internist with an acute exacerbation of chronic back pain. An evaluation did not reveal any neurologic abnormalities. Prior to initiation of nonsteroidal anti-inflammatory drugs (NSAIDs), a laboratory evaluation revealed significant anemia with a hemoglobin of 7.3 g/dL as well as renal insufficiency with a serum creatinine of 3.0 mg/dL. His total protein was not elevated, but his albumin was low at 3.1 g/dL. This constellation of symptoms led to hospitalization and evaluation by a hematologist/oncologist. A serum protein electrophoresis (SPEP), 24-hour urine protein electrophoresis (UPEP), β2 microglobulin (β2M) level, serum free light chain assay, bone marrow aspirate/biopsy, and skeletal survey were performed.

Results showed that all the quantitative immunoglobulins were suppressed. An abnormal band was detected on the SPEP at a concentration of 0.26 g/dL, and immunofixation revealed that this was a free lambda light chain. The UPEP revealed 2830 mg in 24 hours of the free lambda light chain. The β2M was 13.81 mg/L. The serum free light chain assay was markedly abnormal with a free lambda of 4900 mg/L and free kappa of 33 mg/L. Bone marrow biopsy revealed a hypercellular marrow with more than 70% plasma cells, which were proven to be clonal by flow cytometry. Skeletal survey revealed minimal lytic bone disease in the calvarium.

In addition, the creatinine clearance, as measured by the 24-hour urine collection, was 16 mL/minute; calcium was 9.6 mg/dL; and uric acid was normal. Conventional cytogenetics revealed hypodiploidy and deletion of chromosome 13 (del 13). FISH analysis confirmed the del 13. The final Durie-Salmon myeloma stage was 3B and the International Staging System stage was III.

Implications for Physicians

As described elsewhere in this newsletter, acute renal failure accompanying the initial diagnosis of symptomatic myeloma is not uncommon. In determining the optimal course of therapy, it is critical to identify the cause of the renal dysfunction since there are multiple etiologies of renal failure in myeloma, including myeloma cast nephropathy, hypercalcemia, hyperuricemia, dehydration, use of nephrotoxic NSAIDs (often taken to treat bone pain prior to diagnosis), infection, and protein deposition disorders. The patient did not have any signs of dehydration, infection, or hypercalcemia. Protein deposition disorders (amyloidosis or light chain deposition disorder) were unlikely, as those disorders usually present with nephrotic syndrome (as opposed to acute renal failure) and are not usually associated with this level of disease burden.

In the case described above, the apparent cause of the renal failure was light chain cast nephropathy. The goal of initial therapy should be both to reverse the renal failure and to induce a rapid remission. Knudsen et al reported that the main determinant of improvement in survival was the reversal of renal failure, which was more important than response to therapy.1 In this study, reversibility of renal failure was associated with moderate renal failure, hypercalcemia, and low light chain excretion. In addition, this study was performed in an era prior to highly effective novel therapeutics. Those patients who present with profound renal failure secondary to elevated light chains require rapid effective therapy to initially control the myeloma and in turn reverse the renal failure. Kastritis et al recently reported on the efficacy of high-dose dexamethasone with or without novel agents such as thalidomide and bortezomib.2 They demonstrated that high-dose dexamethasone regimens are associated with response to therapy and reversal of renal failure. Those patients who responded to therapy were more likely to have reversal of their renal failure than those patients who did not respond (85% vs 56%; P<0.05). More importantly, when dexamethasone is used with novel agents, the reversal of renal failure occurs more rapidly.

We recently reported on a young patient with light chain myeloma and severe dialysis-dependent renal failure (Gladney SP, Lonial S, Kaufman JL. Clin Lymphoma Myeloma; in press). He was treated with a combination of bortezomib at standard doses, thalidomide, and dexamethasone. He achieved a rapid and sustained remission, with reversal of renal failure. Chanan-Khan et al reported on various bortezomib-based regimens for patients with renal failure requiring dialysis.3 They concluded that bortezomib-based regimens were safe and effective in patients with profound renal failure and eliminate the need for dialysis. Recently, Niesvizky et al reported on the use of lenalidomide...
and dexamethasone as initial therapy for newly diagnosed patients and the impact of renal function on adverse events. They noted that patients with depressed creatinine clearance were more likely to have grade 3 or greater neutropenia and require more frequent dose reductions. The authors did not report on the efficacy of the regimen and reversibility of the renal failure.

Our patient in the case report was treated with the combination of bortezomib, thalidomide, and dexamethasone. After one cycle, the patient’s serum creatinine was 2.0 mg/dL. The serum free light chain ratio normalized, and there was no detectable free light chain in the serum or the urine. The challenge in treating this patient will be to develop an adequate long-term treatment plan in the face of such poor-risk cytogenetics.

References

RENAL INSUFFICIENCY IN MYELOMA PATIENTS: A NURSE’S PERSPECTIVE

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Multiple myeloma (MM) is an overproliferation of plasma cells in the bone marrow, and currently more than 55,000 patients in the United States are living with the disease. The peak occurrence of MM is among people in their 50s through 70s. Common clinical features of symptomatic MM include kidney dysfunction, bone pain, fatigue, recurrent infections, anemia, and hypercalcemia, yet not all features will be exhibited by all patients.

The median age at MM diagnosis is 62 years, and approximately 25% of patients will present with renal insufficiency or renal failure at diagnosis or during their disease. Challenges to treating patients with MM may include older age at presentation and multiple coexisting morbidities, such as hypertension, diabetes, or other chronic health conditions, that may contribute to renal insufficiency. Therefore, for patients with symptomatic MM, careful attention must be paid when selecting an appropriate therapy and supportive care measures. Nurses play a critical role in identifying patients at risk for kidney damage from MM, and by employing appropriate preventative and treatment interventions, can reverse the potentially long-term negative effects that MM may have on the kidneys.

Pathogenesis of renal insufficiency in MM

The glomerulus is responsible for filtering immunoglobulin light chains before the light chains are broken down and excreted through the urine. Light chains that are present in the serum or urine may overwhelm the ability of the proximal tubules to absorb and process the proteins. As the proteins reach the nephrons, light chains will combine with Tamm-Horsfall mucoprotein, which leads to precipitate and subsequent cast formation. On microscopy, there is a characteristic appearance that may be consistent with myeloma kidney. This process will lead to increased serum creatinine levels, decreased glomerular filtration rate (GFR), and increased risk for further deterioration of renal function.

In addition, patients with MM are at risk for renal insufficiency due to other factors. Acute tubular necrosis (ATN) may result from dehydration in the setting of light chain proteins, called kappa or lambda, that may deposit in the kidney as described above. The use of loop diuretics may also 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 non-steroidal anti-inflammatory drug (NSAID) use may also provide insult to the kidneys.

Diagnosis and treatment of renal insufficiency

Renal function can improve and symptoms may even resolve in some patients if problems are detected early; careful observation of laboratory values and symptoms is a key strategy that nurses may employ. Obtaining serum-free light chain assays and routine urine evaluation for Bence-Jones proteins is important in identifying disease progression in patients with secretory and nonsecretory MM who may not be secreting much paraprotein in the serum. Serum chemistry panels to assess for electrolyte abnormalities and impaired renal excretion should also be performed. CBC testing may identify anemia secondary to renal failure. Other
symptoms, such as decreased urinary output or dark urine, may signal that dehydration may be present.

Acute renal failure is evidenced by an elevation of serum creatinine levels of 2.0 g/dL or higher from baseline, and it is important to identify whether this may be related to the disease itself or to other factors as previously described. In most cases, aggressive oral and intravenous hydration may resuscitate the kidneys and aid in excretion of toxic light chains. If the renal failure is due to hypercalcemia, reversal of hypercalcemia by the use of bisphosphonates in addition to hydration may also be indicated; however, caution must be taken as bisphosphonates may also be nephrotoxic. On the other hand, if the renal failure is due to disease progression, reducing tumor burden by initiating dexamethasone pulses may be effective.

There is conflicting evidence as to the efficacy of plasmapheresis, and given only a few small scale studies, this technique remains controversial. Patients with heavy chain disease (such as IgG, IgM, or IgA types of MM) and those with hyperviscosity syndromes may benefit, yet additional randomized controlled trials are required to determine the efficacy of plasmapheresis.7 Dialysis may be indicated if the patient’s GFR is critically low, if the patient is experiencing difficulty maintaining electrolyte levels, and if uremia is becoming an issue.

Factors to consider in relapsed patients with renal insufficiency

Oftentimes, patients with MM experience renal insufficiency due to disease progression. While dexamethasone pulses (dexamethasone 40 mg PO days 1-4) may assist in reversing renal failure due to hypercalcemia or disease progression, the overall survival benefit is not sustained. Fortunately, with the advent of novel therapies within the last few years, there are many options available to treat patients at the time of relapse, even in the setting of decreased renal function, which utilize combination therapies to improve progression-free survival. Thalidomide and lenalidomide are both immunomodulatory agents and have been shown in randomized and controlled clinical trials to be effective at producing remissions in patients with MM. Thalidomide is considered safe in renal insufficiency, and dosage adjustments are not required. Caution must be exercised when using lenalidomide, also an effective agent, as it is excreted mainly through the urine. Renal insufficiency has been linked to increased myelosuppression in patients with decreased creatinine clearance who received lenalidomide therapy.a Despite the absence of clear recommendations, careful monitoring with CBC and differential, as well as basic chemistry panels, must be considered in any patient with a history of renal insufficiency who is receiving lenalidomide.

Bortezomib is a proteosome inhibitor that is FDA approved for use in patients with renal failure; dosage reductions are not necessary. A subset analysis of data from 2 key clinical trials in relapsed MM demonstrated a response rate of 30% in patients with severe renal impairment (evidenced by creatinine clearance <30 mL/min) and 25% in those with moderate renal impairment. In addition, patients with creatinine clearance values as low as 13.8 mL/min have been included in clinical trials.9

Factors to consider in newly diagnosed patients

Frontline therapy in younger patients with decreased renal function may include thalidomide and dexamethasone; vincristine, doxorubicin, and dexamethasone (VAD); or liposomal doxorubicin, vincristine, and dexamethasone (DVD). Alkyating agents, such as melphalan, may be considered for patients not regarded as transplant candidates due to age or other health problems.10 Clinical trials are ongoing utilizing combinations, such as lenalidomide and dexamethasone, and bortezomib and pegylated liposomal doxorubicin (PLD), which also show efficacy in newly diagnosed patients with MM, with promising results. Ongoing clinical trials suggest that the combination of bortezomib and PLD is safe in MM patients with renal dysfunction.

Supportive care

Bisphosphonates, such as zoledronic acid and pamidronate, are potent inhibitors of resorption that stimulate osteoblastic response and promote bone formation. However, bisphosphonate use in patients with renal insufficiency or chronic kidney disease may be toxic to the kidneys, producing renal failure. Caution must be exercised when dosing these drugs, both of which are approved by the FDA for patients with hypercalcemia of malignancy (HCM) and MM.11 Serum creatinine levels once stable can be evaluated at baseline and prior to each infusion of bisphosphonates. Dose reductions of zoledronic acid may also be considered.

Anemia, defined in the patient with MM as a hemoglobin value 2 g/dL below the institutional limits of normal, may be noted in patients with moderate to severe renal dysfunction but may also be an indicator of blood loss, a side effect of cytotoxic therapy, or a result of increased disease activity. If blood loss is not noted, and the anemia is not considered to be related to treatment or disease progression, assessing serum erythropoietin, iron, and vitamin B12 levels may identify the type of anemia present. Using erythropoiesis-stimulating agents (ESAs), such as darbepoetin and erythropoietin, and correcting iron or vitamin deficiency may be effective in managing anemia, which may help improve energy levels and quality of life.12

Monitoring

It is essential for nurses and clinicians to closely monitor patients with MM and renal insufficiency by ensuring that patients obtain routine blood chemistry and CBC testing. While the frequency of this testing is dependent on the degree of renal failure or renal recovery, as well as the response to therapy, it is reasonable to test lab parameters on a monthly basis at minimum.

Conclusion

Renal insufficiency and chronic kidney disease in patients with multiple myeloma should be assessed at initial diagnosis and throughout therapy. Nurses have the
unique ability to play a key role in early identification of renal damage and in educating our patients on preventative interventions such as liberal oral hydration and avoiding NSAID therapy. In addition, by ensuring that patients undergo routine laboratory evaluation with attention to serum calcium and creatinine levels, acute renal failure may be avoided. Prompt intervention with hydration and identification of the underlying cause of renal failure may allow the patient’s renal function to return to near baseline, permit patients more therapeutic options, and provide the potential for longer survival and improved quality of life.

References

Renal Insufficiency in Multiple Myeloma: A Pharmacist’s Perspective

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Renal dysfunction is a common finding in patients with multiple myeloma (MM), and a proportion of these patients require dialysis support. A significant number of patients can experience improvement or normalization of renal function with effective myeloma therapy.1 However, the presence of renal dysfunction can make choosing drug therapy challenging considering the many drugs that are eliminated primarily by the kidneys. Care must be taken in order to optimize drug therapy for the many patients with MM who also have renal insufficiency.

Many regimens have been used for treatment of multiple myeloma. Melphalan-prednisone has been used for more than 20 years in patients who are not candidates for autologous stem cell transplantation. The corticosteroid prednisone is active in multiple myeloma and does not require dosage adjustment in renal impairment. Melphalan is partially cleared by the kidneys and does require dosage adjustment in patients with renal insufficiency. This was demonstrated in a retrospective analysis of patients treated with melphalan without dose adjustments for renal impairment. The study showed a negative correlation between creatinine clearance (CrCl) and hematologic toxicity.2 Another regimen that has been used for many years is the combination of vincristine, doxorubicin, and dexamethasone (VAD). This regimen can be used as induction therapy in patients who may undergo autologous stem cell transplantation. Because none of the agents in VAD rely upon the kidneys for clearance, this combination can be used without dose reduction in MM patients with renal insufficiency. Furthermore, following induction therapy, autologous stem cell transplantation has proven feasible in patients with renal impairment.3-5

More recently, several drugs, including bortezomib, thalidomide, and lenalidomide, have moved to the forefront of multiple myeloma treatment. Bortezomib is a proteasome inhibitor that is approved for relapsed or refractory multiple myeloma. Several reports describe improvement of renal impairment in patients treated with bortezomib-based regimens.6-9 Although the extent of renal excretion of bortezomib is not entirely known, it does not appear to cause unexpected toxicity in patients with renal insufficiency. While a dose reduction may be considered in patients with poor performance status or additional comorbidities, it is likely not necessary in patients with isolated renal dysfunction, including those undergoing hemodialysis.8-9

Thalidomide and lenalidomide are oral immunomodulatory agents with antineoplastic and antiangiogenic properties. Very little thalidomide is excreted in the urine as unchanged drug, and toxicity in patients with renal dysfunction appears comparable to that seen in patients without renal dysfunction.10,11 However, caution should be taken when initiating thalidomide in patients with renal impairment due to several cases of severe hyperkalemia in this population.12 Low starting doses (ie, 100 mg) with dose increases as tolerated should be utilized and potassium should be monitored. The mechanism for this potential adverse effect is unknown. In contrast to thalidomide, the elimination of lenalidomide is highly dependent on renal excretion. Cre-
Renal function should be evaluated prior to initiating pamidronate and 15 minutes for zoledronic acid. Administration times should be no less than 2 hours for pamidronate, the currently used monthly dose.19 In patients with multiple myeloma, doses should be initiated and adjusted carefully, taking into account patient-specific response and toxicities to treatment. With careful monitoring, effective drug therapy can be safely given to this population.

References
1. Which of the following statements is FALSE?
   a. Renal impairment represents one of the major complications of multiple myeloma (MM)
   b. As many as 50% of patients with MM require dialysis because of severe renal impairment
   c. Up to 50% of patients newly diagnosed with MM have a decrease in creatinine clearance, and approximately 30% of patients have a serum creatinine level equal to or higher than 1.5 mg/dL at the time of diagnosis
   d. The severity of renal impairment significantly affects the prognosis of patients with MM, and renal dysfunction has been associated with shorter survival

2. Which of the following may be useful in detecting renal dysfunction in patients with MM?
   a. Serum-free light chain assays and routine urine evaluation for Bence-Jones proteins
   b. Serum chemistry panels to assess for electrolyte abnormalities
   c. Complete blood count (CBC) testing
   d. All of the above

3. Which of the following interventions would NOT be helpful in improving the renal function of MM patients?
   a. High-dose potassium supplementation
   b. Avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs)
   c. Routine laboratory evaluation with attention to serum calcium and creatinine levels
   d. Prompt and liberal oral hydration

4. Melphalan-based chemotherapy and high-dose chemotherapy with autologous stem cell transplantation have limitations in MM patients with renal failure because of which of the following?
   a. Suboptimal survival benefits and early mortality
   b. Excessive toxicities
   c. The need for dose reductions and treatment discontinuations
   d. All of the above

5. Which of the following reasons explains why the combination of vincristine, doxorubicin, and dexamethasone (VAD) can be used as induction therapy without dose reduction in MM patients with renal insufficiency?
   a. Because no toxicities are associated with the VAD regimen
   b. Because none of the agents in VAD rely upon the kidneys for clearance
   c. Because the VAD regimen is cleared mainly through the kidneys
   d. None of the above

6. To help prevent bisphosphonate-induced renal dysfunction, which of the following has been recommended?
   a. Dose reduction
   b. Longer infusion time
   c. Reduction in dose frequency
   d. All of the above

7. Since their introduction in the 1990s, two immunomodulatory agents have shown efficacy, alone or in combination with dexamethasone, in the overall population of MM patients. What are the names of these agents?
   a. Bortezomib and lenalidomide
   b. Thalidomide and bortezomib
   c. Thalidomide and lenalidomide
   d. Bortezomib and thalidomide

8. Caution should be exercised when initiating thalidomide in MM patients with renal impairment due to which of the following?
   a. The high rate of treatment discontinuations in this population
   b. Several cases of severe hyperkalemia in this population
   c. Birth defects
   d. None of the above

9. Which of the following statements is TRUE?
   a. The elimination of thalidomide, but not that of lenalidomide, is highly dependent on renal excretion
   b. The elimination of both lenalidomide and thalidomide is highly dependent on renal excretion
   c. The elimination of lenalidomide, but not that of thalidomide, is highly dependent on renal excretion
   d. The elimination of neither lenalidomide nor thalidomide is highly dependent on renal excretion

10. At ASH 2007, Parikh et al reported on the outcome in 48 patients who received ASCT for MM while in renal failure. Which of the following was among the authors’ conclusions?
    a. Response rates and outcomes for MM patients in renal failure were similar to those observed in other MM patients
    b. ASCT after high-dose therapy is safe and feasible in patients with MM and renal failure
    c. Approximately 35% of patients had a significant improvement in renal function after transplant
    d. All of the above
To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
1 = Strongly Disagree   2 = Disagree   3 = Neutral   4 = Agree   5 = Strongly Agree

**Extent to Which Program Activities Met the Identified Objectives**

After completing this activity, I am now better able to:

Describe the prevalence of renal insufficiency among patients with MM

Recognize the special challenges in pharmacologic treatment of the many patients with MM who also have renal insufficiency, especially those requiring dialysis

Discuss the results of studies showing treatments that are active and safe in MM patients with renal impairment, including those with advanced renal failure requiring dialysis

**Overall Effectiveness of the Activity**

The content presented:

Was timely and will influence how I practice

Enhanced my current knowledge base

Addressed my most pressing questions

Provided new ideas or information I expect to use

Addressed competencies identified by my specialty

Avoided commercial bias or influence

**Impact of the Activity**

Name one thing you intend to change in your practice as a result of completing this activity:

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Please list any topics you would like to see addressed in future educational activities:

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EVALUATION FORM

Considerations in Multiple Myeloma: Renal Dysfunction
Project ID: JE8027115

Additional comments about this activity:
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As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

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Posttest Answer Key

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