Achieving an Early Myeloma Response in Patients With Kidney Impairment

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There is increasing evidence, particularly in severe acute kidney injury, that treatment of multiple myeloma with regimens that include dexamethasone in combination with novel chemotherapy agents are associated with an early disease response in most patients. However, the evidence to guide the optimal chemotherapy regimen in patients with kidney impairment is limited, and treatment choices are complicated by the effect of kidney function on drug dosing. Here, we summarize the current status of this field, with a particular focus on chemotherapy regimens that are based on dexamethasone and novel agents and an outline of those areas in which further work is needed to improve the evidence base.

Key Words: Myeloma, Renal impairment, Treatment response

Introduction

Multiple myeloma (MM) is characterized by a clonal proliferation of plasma cells resulting in end organ damage. At presentation, up to 50% of patients will have some degree of renal impairment; up to 10% may require dialysis support.[1-3] Although there are several patterns of kidney injury in MM, the most common lesion is cast nephropathy (myeloma kidney), which is a direct consequence of high levels of circulating clonal serum immunoglobulin free light chain (FLC).[4] There is an increasing focus on management of the FLC load, predominantly through chemotherapy, accompanied by high-quality supportive care.[5]

Although MM remains an incurable disease, the median survival of patients has increased from 29.9 to 44.8 months over the last decade[6]; a principal reason for this improvement has been the introduction of the "novel" agents. However, kidney impairment (KI) remains a major determinant of poor outcome in patients with MM. This particularly applies to patients with severe kidney disease as defined by an estimated glomerular filtration rate (GFR) of less than 15 mL/min. Patients who require and remain dialysis-dependent have a median survival of less than 1 year.[7] The outcome of these patients is improved by recovery of kidney function and long-term dialysis independence, and this improvement in outcome is dependent on the depth of response[8] and an early disease response.[9-11] In this review, we discuss the evidence for the relationship between kidney function and outcomes in patients with MM and focus on the current status of disease-specific treatment in this area.

The Relationship Between Kidney Function and Outcomes in Patients With MM

Recent studies have confirmed the relationship between dialysis dependency and poor outcomes in people with MM.[10,12,13] What is less certain is the effect of kidney disease of lesser severity. One of the major confounders in this area is that the relationship between kidney function and disease burden, and data are conflicting. In univariate analysis, kidney failure has been shown to be associated with inferior survival, but this is not always borne out in multivariate analysis.[14,15] However, a recent study that reported data on 387 patients showed that CKD Stage 4–5 (comprising approximately one third of the patients included in the study) was associated with worse survival as a risk factor that was independent of disease severity.[16]

What Is "Response" in Myeloma Patients With Kidney Injury?

"Kidney" Response

There continues to be disagreement on the best measure of kidney function in myeloma patients. The Modification of Diet in Renal Disease formula currently appears to be the most commonly referred to measure, and despite its inaccuracy when the true GFR is above 60 mL/min and its lack of validation in certain key clinical settings (eg, myeloma) it is accepted as standard in the International Myeloma Working Group (IMWG) guidance. Methods for defining kidney response were recently published in a consensus statement by the IMWG, these

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describe kidney response in terms of complete kidney response, partial kidney response, and moderate kidney response.[8] The group recommended that a complete response should be described as an improvement in estimated GFR (eGFR) from less than 50 to greater than 50 mL/min after treatment, a partial response as an improvement in eGFR from less than 15 to 3059 mL/min after treatments, and a mild response as an improvement in eGFR from less than 15 to 15—29 mL/min after treatment.[8] This definition is not without limitations, it is based on the classification system for CKD in what is often a setting of acute kidney injury and assumes that only patients with certain baseline eGFR can have certain levels of response. As a consequence, defining "kidney response" remains problematic. That accepted, suggested kidney responses that are based on the Modification of Diet in Renal Disease formula have been published.[8]

An important recent paper by Ludwig and colleagues[17] assessed the relationship between disease response and kidney response (improvement in kidney function) in patients with MM and KI. They showed that an improvement in kidney function, using eGFR, correlated with the response of the tumor to chemotherapy, with the greatest kidney response (as defined by an improvement in eGFR to >50 mL/min) seen in patients obtaining a complete, near complete, or very good partial response. The study reported that baseline eGFR and tumor response correlated with kidney response, and pretreatment clinical status, lactate dehydrogenase, and tumor response correlated with survival. The patients in this study were treated with a bortezomib-, doxorubicin-, and dexamethasone-based regimen.

CLINICAL SUMMARY

- Patients with kidney impairment at the time of presentation with myeloma have poorer survival than those with preserved kidney function.
- Those patients with dialysis-dependent kidney failure at presentation have a better prognosis if they recover independent kidney function; this improved prognosis is related to rapid reduction in light-chain levels.
- There is evidence that regimens that include novel agents (particularly bortezomib) combined with dexamethasone have improved kidney outcomes for patients with kidney impairment at presentation.

Myeloma Response

Uniform response criteria have been published by the IMWG. The uniform response criteria defined by the group are shown in Table 1. Kidney response is not a criterion for myeloma response in these guidelines: Given the influence of KI in the prognosis of patients with MM, it could be argued that greater emphasis on kidney response should be included.[18]

Time to response is not yet an accepted outcome measure. However, it may yet turn out to be a critical outcome measure in patients with cast nephropathy. One of the most important observations in recent open-label studies of patients with MM and severe acute kidney impairment (AKI) is that improvements in serum FLC levels in the first 3 weeks, and in some patients as early as 12 days, after the initiation of chemotherapy are associated with increased rates of recovery of kidney function.[9-11] Most of the patients who were included in these studies were dialysis-dependent and had new diagnosis of MM. Randomized controlled trials of high cutoff dialysis and bortezomib-based chemotherapy regimens are currently underway[19]; if these confirm the relationship between early improvements in FLC levels and kidney recovery, then they may form the basis for studies addressing the hypothesis that early changes in chemotherapy regimens in this setting in patients who do not have an early disease response remain dialysis-dependent may increase the likelihood of kidney recovery.

Although the association between serum FLC levels and recovery from severe AKI is of great interest, it is not known if an early disease response as measured by an early decrease in serum FLC from baseline has utility in patients with less severe KI. This is a potentially important area. Because of the toxicity of clonal FLC to the kidney,[4,20] strategies that are focused on a rapid decrease in serum FLC levels may reduce the potential for further kidney injury and optimize kidney function because yet unpublished data from the MERIT study suggest a 6.6% improvement in survival for each log percentage reduction in FLC level. The design of any studies of this type will ultimately depend on confirmation of the relationship between improvement in kidney function and clinical outcomes after response to chemotherapy; this is not yet known and should be a focus of further studies.

Does Early Recognition and Commencement of Disease-Specific Treatment Improve Clinical Outcomes?

A large U.S.-registry-based study examining the time between first presentation with a symptom attributable to MM and confirmed diagnosis of the disease showed that patients who were more likely to suffer a delay in diagnosis were older, had multiple comorbidities, and were of nonwhite ethnicity. This study did not consider if an initial presentation with KI was associated with diagnostic delay.[22] However, in a U.K.-based study, the time from first presentation to diagnosis was more than 3 months in 70% of patients: 7% of patients initially presented to nephrologists and 50% of had a delay in excess of 6 months