In Focus

To biopsy or not to biopsy, that is the question in myeloma cast nephropathy

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In 2003, the International Myeloma Working Group (IMWG) recognized renal insufficiency [serum creatinine (Scr) > 173 μmol/L] as a myeloma-related organ impairment in their first consensus diagnostic criteria for multiple myeloma (MM) [1]. In 2006, CRAB [hyperCalcemia, Renal impairment (RI), Anemia and Bone lesions] became the official myeloma defining events (MDEs) [2]. Of the four MDEs, RI by far exacts the worse prognosis. Data from a Spanish study showed that patients presenting with RI as their MDE had a much shorter survival than patients who did not. The median overall survival (OS) was 8.6 months for the RI patients versus 34.5 months in patients who presented with other MDEs (P < 0.001) [3]. Similar findings were reported in a Nordic study that found the OS for severe RI (Scr > 2.28 mg/dL), moderate RI (Scr > 1.48 and ≤2.28 mg/dL) and no RI were 13, 18 and 36 months, respectively [4]. The Nordic study was slightly different in that smoldering MM was not excluded. Even more interesting was that the negative impact of RI was not permanent. In both studies, patients who recovered renal function to a Scr of <1.5 mg/dL had OS similar to those who never developed RI [3, 4]. Lower response to chemotherapy was noted in the RI patients in the Spanish study but only in those who died within the first 2 months. No differences in response were noted in the Nordic study when the patients were evaluated at 12 months. In the Nordic study, the hematologic response was not associated with a renal response (P = 0.07).

The biggest advancement in the care of MM is the introduction of novel agents (thalidomide, lenalidomide, pomalidomide, bortezomib and carfilzomib) capable of delivering faster and deeper responses with less toxicity. Of the novel agents, bortezomib has shown the greatest benefits in RI patients. In the phase III VISTA trial, the addition of bortezomib to melphalan and prednisone significantly improved both the hematologic response, renal recovery and OS without increasing the adverse events in patients with an estimated glomerular filtration rate (eGFR) of <50 mL/min [5]. In a retrospective analysis of MM patients from 1990 to 2005 and beyond, improvement of OS was seen with each successive 5-year period. In patients with severe RI (<30 mL/min/1.73 m²), age (> or <65 years) and the class of novel agent were independent risk factors [6]. The largest benefit was seen in younger patients and those treated with bortezomib. Early (<2 months) death was still highest among patients with severe RI (12%) versus moderate RI (7%) and no RI (3%), and the incidence did not change over time. In a subgroup analysis of the randomized HOVON-65/GMMG-HD4 trials, patient treated with a vincristine-based regimen had a 3-year survival of 76% if their presenting Scr was <2 mg/dL versus 34% if the presenting Scr was ≥2 mg/dL [7]. In comparison, the 3-year OS (74%) in the bortezomib-treated patients was not significantly different regardless of their presenting Scr. Bortezomib-treated patients with RI had a hematologic response rate of 75% versus 36% in the vincristine-treated group. Interestingly though, both RI groups still had a significantly higher early mortality regardless of the treatment arm. Thus, while the long-term effects of RI appeared to be reversed, the early mortality remained a challenge.

Until recently, RI in MM was mainly defined by the creatinine concentration. The 2010 IMWG definition included the toxic effects of the monoclonal light chains, but the acute kidney injury (AKI) was neither differentiated by the renal lesion nor by the causes such as hypercalcemia or nephrotoxins [5]. There is now a growing body of evidence showing that different renal lesions behave differently in MM. Patients with pure monoclonal immunoglobulin deposition disease (MIDD) have better renal and OS than patients with both MIDD and myeloma cast nephropathy (MCN) [8]. This observation has been confirmed in a larger series of patients with MCN, MIDD or...
both where those with MCN had the worst renal and survival outcomes [9]. The renal lesion was also important in determining renal response. Rapid reduction of the serum free light chain (sFLC) has now been viewed as the most important factor for the recovery of renal function in MM but only in patients with MCN [10, 11]. Due to the differences in clinical presentation and response, the IMWG updated their diagnostic criteria to stress that renal impairment should be due to MCN rather than other renal lesions that may be associated with MM [12].

Given the importance of the renal lesion, renal biopsy plays a vital role in the diagnosis and study of MM patients with AKI. A renal biopsy is recommended in patients with a high degree of albuminuria to rule out immunoglobulin light-chain (AL) amyloidosis or MIDD [13, 14]. Furthermore, patients with sFLC levels <500 mg/L should also undergo a kidney biopsy as MCN is unlikely [12]. However, when the diagnosis of MCN seems certain, a renal biopsy is not recommended. In the current issue of *Nephrology Dialysis Transplantation*, the manuscript by Ecotière et al. provides evidence of why a renal biopsy may be helpful even when MCN seems certain. In a highly selected group of patients (all of whom had MCN), the authors found that a significant portion of patients had secondary renal pathologies. These included eight cases of coexisting MIDD, three cases of AL amyloidosis and nine cases of focal segmental glomerulosclerosis, which occurred at a rate much higher than previously thought [15]. Moreover, the authors found the renal biopsy had prognostic importance. While the reduction of the pathologic sFLC remained the most important predictor for recovery of renal function, in patients who achieved a hemato logic response, the number of casts per biopsy and tubular atrophy was significantly associated with renal response [10, 11]. The number of casts on a biopsy has been reported in previous reports but has not been a consistent finding [16–18]. The results from this study certainly add to the evidence. Finally, the risk of the renal biopsy in this study was small, similar to previous reports in the literature [19, 20].

One of the main reasons for a more conservative recommendation on renal biopsy was the concern over the risk of bleeding. In particularly, patients with amyloidosis (not uncommon in this population) were thought to have a higher risk of bleeding. This misconception has fortunately been refuted by two studies that demonstrated the risk of post-biopsy hemorrhage was ~4% and was no different than patients without amyloidosis [19, 20]. Therefore, it is possible to safely perform a renal biopsy in patients with MM as long as the patient does not have other risk factors for bleeding. This was noted in the current study where none of the 70 patients had a severe bleed after the kidney biopsy.

The field of medicine advances as a result of the science, but it has always been practiced as an art. Nowhere is this more apparent than in the care of MM patients with AKI. In regard to kidney biopsy, the manuscript by Ecotière et al. has definitely provided good data to support the procedure even in cases where MCN seems certain. A renal biopsy was found to be safe, beneficial in predicting renal response in hematologic responders and added to our scientific knowledge. So, should a renal biopsy be performed the next time we face a patient with MM and AKI? That is where the art comes in. The benefits must be balanced by the cost, the risk and the added benefits to the patient. In the end, it is our ability to possess compassion for our patients, to hope for their well-being, to deviate from the norm in order to accommodate their individual needs and desires that separates us from logic-based programs that some feel one day could replace the physician. With the charge to make medicine more evidence based, it is easy to let the science dominate over art. As doctors, it is our job to marry the two sides so that our patients may not only see but to enjoy another midsummer night’s dream.

### CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Ecotière et al. Prognostic value of kidney biopsy in myeloma cast nephropathy: a retrospective study of 70 patients. *Nephrol Dial Transplant* 2016; 31: 64–72.)

### REFERENCES

Cell-cycle arrest biomarkers: the light at the end of the acute kidney injury tunnel

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For many years, terms such as acute renal failure, acute tubular necrosis and acute kidney disease have been used to identify a group of disorders in which oliguria and an increase in serum creatinine were the final common findings. A more sophisticated and articulated definition of the abrupt decline in renal function was reached when the term acute kidney injury (AKI) started to be applied. Today we are facing a new era in which the possibility of molecular diagnosis of disease implies a careful evaluation of all aspects of a clinical disorder, including organ dysfunction and tissue damage. The impact of this approach is enormous since it may allow early identification of patients subject to damage progression or complete organ dysfunction, ultimately affecting clinical outcomes such as morbidity, mortality and dialysis requirement in the case of the kidney. There is now a common consensus that the development of AKI depends on the condition of the organ (susceptibility) and the intensity of the insult (exposure).

AKI is a complex disorder with important consequences in terms of morbidity and mortality. AKI is also an important concern for healthcare systems since it may represent a path towards chronic kidney disease (CKD) [1]. Clinicians are subject to many challenges when dealing with AKI patients. These challenges include the identification of patients at risk and evaluation of the susceptibility of the kidney to exposures, the need for early recognition of injury/dysfunction of the target organ and monitoring of progression towards severe dysfunction, chronic disease or possible recovery. These challenges are even more pronounced when critical illness is present and other conditions such as sepsis are involved [2]. In this evolving area of research and care, the process of implementation of new biomarkers is becoming crucial. The process of discovery has been conducted by evaluation of several molecules that are expressed in the blood or urine of patients with AKI. In this case, candidate biomarkers have been studied, selecting the most suitable molecules. Furthermore, the pathophysiological plausibility of candidate biomarkers’ involvements in the damage process has been elucidated under experimental and clinical conditions. The subsequent step was validation, where specific molecules have been evaluated prospectively in a cohort of patients to elucidate their capacity to predict the occurrence of a certain event or even to identify individuals at risk to develop the syndrome. We are far from the times in which one could accept a 60% chance to predict an event. New biomarkers should be capable of offering predictive capabilities >80 or even 90%.

In spite of a growing body of publications, many new biomarkers have not satisfied these requirements and most have