

## Managing Myeloma Kidney

It is estimated that, in 2005, multiple myeloma will be diagnosed in 15 980 persons and 11 300 persons will die of it, constituting 2% of all deaths from cancer (1). Although myeloma bone disease and anemia are the primary manifestations of the disorder, only 52% of patients have normal renal function at diagnosis. At presentation, the serum creatinine level is between 114  $\mu\text{mol/L}$  (1.3 mg/dL) and 175  $\mu\text{mol/L}$  (2.0 mg/dL) in 29% of patients and 176  $\mu\text{mol/L}$  or more ( $\geq 2.0$  mg/dL) in 19% of patients. Therefore, nearly 8000 patients per year will present their physicians with the challenging problem of managing the renal impairment associated with myeloma (2). In many instances, the renal insufficiency associated with multiple myeloma is related to several reversible problems due to volume depletion; hypercalcemia; and exposure to contrast material, nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors (3, 4). However, the most common finding is cast nephropathy (5, 6).

In cast nephropathy, filtered immunoglobulin light chains bind to a common site on Tamm–Horsfall protein. Tamm–Horsfall glycoprotein is secreted by the thick ascending limb of Henle loop and may function as a unique renal mechanism to regulate several potent cytokines, including interleukin-1 and tumor necrosis factor. Aggregation of these protein–protein complexes produces casts that physically obstruct tubule fluid flow, resulting in renal failure (7). Patients with a higher excretion of monoclonal immunoglobulin light chains in the urine have renal failure considerably more often than patients with lower excretion levels (8). Patients with myeloma that produces only intact immunoglobulins rarely develop cast nephropathy because the entire immunoglobulin molecule is too large to pass through the glomerular filter. Shortening the time in which the patients' kidneys are exposed to toxic light chains lowers the risk for permanent renal insufficiency. Therefore, reducing urinary light chain excretion is an urgent priority.

The standard therapy for cast nephropathy has been plasma exchange. The rationale for plasma exchange is to reduce serum light chain levels, while chemotherapy reduces the number of light chain-secreting malignant plasma cells. In this issue, Clark and colleagues' study (9) challenges this widely held standard of patient management.

The finding of renal insufficiency with light chains in the urine is not necessarily diagnostic of "myeloma kidney." The differential diagnosis of renal insufficiency and light-chain proteinuria includes amyloidosis, Fanconi syndrome, crystalline nephropathy, cryoglobulinemia, and Randall-type light-chain deposition disease. To distinguish among these, renal biopsy may be necessary (10, 11).

When renal failure due to cast nephropathy occurs, it dominates the subsequent clinical course of multiple my-

eloma. Among 375 000 patients in the U.S. Renal Data System who are receiving end-stage renal disease therapy, 3300 (0.88%) patients had myeloma nephropathy. The 2-year all-cause mortality rate in myeloma nephropathy was 58%, and myeloma nephropathy was independently associated with decreased survival (12). In a study of 775 patients with multiple myeloma, those who needed dialysis had a poor prognosis with a median survival of only 3.5 months. Reversal of myeloma nephropathy occurs in 50% of patients and is associated with better long-term survival. A landmark analysis showed that reversal of renal failure was a more important prognostic factor than response to chemotherapy (13, 14). The presence of renal failure also affects the outcome of therapy in multiple myeloma. Induction therapy followed by autologous stem-cell transplantation prolongs survival. Patients with a glomerular filtration rate that is less than normal have a substantially shorter post-transplantation survival of 5.1 years, and a normal glomerular filtration rate is predictive of a longer mean survival of 7.5 years (15). Patients with persistent renal impairment who receive a stem-cell transplant also have longer hospitalizations, increased use of blood products, and increased numbers of infections. The transplantation-related mortality rate is as high as 17% in patients with myeloma and renal insufficiency but is 1% if renal function is normal (16).

The recognition that patients whose renal function normalizes have better outcomes led to attempts at reversing tubular toxicity. Several small trials using alkylator-based chemotherapy (primarily melphalan) have suggested that plasma exchange has value. In a randomized study (17), half of patients received standard dialysis and the other half received plasma exchange. Plasma exchange was more effective than dialysis for reducing light chain proteinuria and leading to renal recovery (17). Of these patients, 15 were randomly allocated to plasma exchange, corticosteroids, and chemotherapy and 14 were randomly allocated to dialysis, corticosteroids, and chemotherapy. Renal function recovered in 13 of the 15 patients receiving total plasma exchange and in 2 of the 14 patients who did not receive plasma exchange. Plasma exchange with chemotherapy reduced the light chain burden and improved renal function (18). In another study of 21 patients with active myeloma and progressive renal failure (all treated with melphalan), 10 were randomly assigned to chemotherapy and diuresis and 11 were randomly assigned to the same regimen with plasma exchange. Plasma exchange incurred a slight benefit. The severity of cast formation as seen on kidney biopsy was predictive of outcome (19). In a retrospective, uncontrolled series of 26 patients with rapidly progressive renal failure, plasma exchange was associated with lower rates of starting or continuing dialysis (20). Taken together, these findings led an expert panel of the

Scientific Advisors of the International Myeloma Foundation to conclude that plasma exchange could be “critically important” in the management of myeloma kidney (21).

In this issue, Clark and colleagues (9) report a trial in which they randomly assigned 104 patients in 14 participating centers. Conventional therapy consisted of either melphalan–prednisone for 4 days every 4 weeks or infusional vincristine–doxorubicin–dexamethasone (VAD) every 4 weeks, at the clinicians’ discretion. In addition to conventional therapy, the exchange group received 5 to 7 plasma exchanges of 5% serum albumin. The primary statistical end point was a composite variable of death, dialysis dependence, or glomerular filtration rate less than  $0.29 \text{ mL} \cdot \text{s}^{-2} \cdot \text{m}^{-2}$  ( $<30 \text{ mL/min per } 1.73 \text{ m}^2$ ) at 6 months. The study did not demonstrate improvement with plasma exchange. Of the patients, 69.2% in the control group and 57.9% in the plasma exchange group experienced the composite end point (between-group difference, 11.3% [95% CI,  $-8.3\%$  to  $29.1\%$ ]). Although the trial was the largest ever conducted, the CI for the difference in the composite end point was wide, which shows that the trial results were compatible with a substantial difference in either direction. Dialysis dependence at 6 months was twice as frequent in the control group as in the plasma exchange group (27% vs. 13%). The difference was 14.1 percentage points (CI,  $-5.1$  percentage points to  $34.6$  percentage points). The wide CI shows that the study, despite its size, was underpowered.

Could Clark and colleagues have missed a clinically important benefit for a subgroup of severely affected patients? The study began before introduction of the immunoglobulin-free light chain assay (22), which is a much improved method for quantitating small amounts of light chain in serum specimens. Thus, the authors could not test for a possible correlation between the serum levels of circulating light chain and benefit from plasma exchange. In the relatively small study, proving differences in a subgroup of patients would be difficult because of statistical uncertainty in analyzing differences in subgroups of patients. The hypothesis that plasma exchange could selectively benefit those patients with cast nephropathy and extreme elevation of serum light chain levels is still plausible. Despite these limitations, the study is the best-designed study to date and is by far the largest. The study does not support the use of plasma exchange in the presence of cast nephropathy.

Why did earlier reports suggest plasma exchange has a benefit that Clark and colleagues’ larger study did not confirm? Plasma exchange is nothing more than a temporizing measure, physically lowering levels of serum light chains, while systemic chemotherapy reduces the production of light chain by eliminating the myeloma cells responsible for their production. Previously, the standard chemotherapy for myeloma was melphalan and prednisone (low-intensity steroids). This regimen acts slowly, with a median time to response ranging from 4 to 6 months. Today, high-

dose dexamethasone, whether part of a VAD regimen or combined with novel agents, is first-line therapy (in Clark and colleagues’ study, 43 patients received VAD). Dexamethasone-based regimens produce responses in as short a time as 0.7 month. A rapid response after treatment reduces the duration of tubule exposure to toxic light chains. Plasma exchange may not benefit patients who are treated with high-intensity corticosteroids but may benefit patients who are treated with melphalan–prednisone. The VAD-treated group did not have better outcomes than the melphalan–prednisone group in Clark and colleagues’ study, so the reasons why this study did not confirm earlier work are speculative.

In summary, despite 20 years of use and the formal endorsement of the Scientific Advisors of the International Myeloma Foundation (21), plasma exchange for managing acute renal failure in multiple myeloma can no longer be routinely recommended.

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