Extracorporeal Removal of Light Chains: New Data and Continued Controversies

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Multiple myeloma represents 1% of all cancers and 15% of hematologic malignancies (1). Despite improvements in outcomes for this disease over the past several decades, the 5-year survival rate is still only 50%.

Kidney dysfunction is common in myeloma, and it is present in 40% of patients at diagnosis; close to 15% of patients require dialysis at the time of presentation (2). The most common etiology is AKI from cast nephropathy. Patients with cast nephropathy have poorer 1-year survival compared with patients without kidney involvement. This poor prognosis is reversible if kidney function is restored (3). The primary mechanism of kidney injury is coprecipitation of filtered free light chains with Tamm–Horsfall protein in the distal tubules.

With melphalan- and cyclophosphamide-based chemotherapy used in the past, reduction of serum free light-chain concentrations was gradual, and kidney recovery and dialysis independence were infrequent. With the advent of newer therapeutic agents, particularly the proteasome inhibitor bortezomib, the reduction of serum free light-chain concentrations is more rapid, and kidney recovery is significantly improved. However, the overall rate of hemodialysis independence remains poor, with response rates of 30% in most series.

Recognition that rapid reduction in the concentration of free light chains is associated with improved kidney outcomes in patients with cast nephropathy has led to a renewed interest in extracorporeal methods of free light-chain removal (4).

The application of extracorporeal therapy for cast nephropathy initially began with the use of plasmapheresis as a means of free light-chain removal. Although several trials reported improved kidney recovery, the data were severely flawed. The largest randomized, controlled trial of plasmapheresis for treatment of presumed cast nephropathy was reported over a decade ago (5). This study randomized 104 patients to either standard medical care (pre-bortezomib era) or five to seven plasmapheresis sessions in addition to standard of care. There was no difference between the two groups in the composite end point of death, dialysis, or reduced kidney function at 6 months. This trial has been criticized, because the sample size was small; also, there was no biopsy confirmation of cast nephropathy. More recently, high-cutoff hemodialysis has emerged as a means of extracorporeal removal of free light chains as an adjuvant to chemotherapy in the treatment of cast nephropathy. Prolonged dialysis (6- to 8-hour sessions) is performed with a hemodialyzer with a large pore size (45–60 kD). In vitro studies showed that high-cutoff hemodialysis could achieve removal of 90% of free light chains over a 3-week period (6). Retrospective studies using high-cutoff hemodialysis showed significant reductions in free light-chain concentrations and improved kidney function. In patients with biopsy-

confirmed severe cast nephropathy treated with and extracorporeal therapy (high-cutoff hemodialysis or plasmapheresis) and either bortezomib or thalidomide, a 60% reduction in serum free light-chain concentrations within 21 days was associated with kidney recovery in 80% of patients; in patients receiving dialysis, 63% became dialysis independent. In the largest study of 67 patients on dialysis treated with high-cutoff hemodialysis, 63% of patients became dialysis independent (7). However, this and all previous trials were conducted during the era of bortezomib based chemotherapy, and they lacked randomization and control patients. To address this inadequacy, two randomized, controlled trials using high-cutoff hemodialysis have now been completed.

In the Multiple Myeloma and Renal Failure due to Myeloma Cast Nephropathy (MYRE) Trial, a total of 98 patients with biopsy-confirmed cast nephropathy requiring dialysis were randomized to either intensive high-flux hemodialysis or high-cutoff hemodialysis (eight sessions of 5 hours in duration over the first 10 days and then thrice weekly in both groups) (8). Patients initially entered a screening period that involved administration of high-dose steroids; correction of volume depletion and other precipitating factors, such as hypercalcemia; and kidney biopsy. Patients with cast nephropathy who required dialysis were subsequently randomized after the screening period. All patients received bortezomib-based chemotherapy. There was no significant difference in the primary end point of dialysis independence at 3 months between the control and high-cutoff hemodialysis groups (33% versus 43%, respectively; P50.42), although the median reduction rate of free light chains after the first dialysis session was significantly higher in the high-cutoff hemodialysis group (68%) compared with the control group (31%; P50.001). The rate of kidney recovery in the control group was similar to that reported in retrospective studies in patients treated with bortezomib-based chemotherapy regimens alone (30%–50%). In secondary analyses, significantly more patients in the high-cutoff hemodialysis group were dialysis independent at 6 months (56.5% versus 35.4%; P50.04) as well as 12 months (60.9% versus 37.5%; P50.02). Dialysis independence at 12 months was associated with a decrease in serum free light-chain concentration to ,500 mg/L with the first round of chemotherapy (P50.01) and randomization to high-cutoff hemodialysis (P50.02). Overall, this study may have been underpowered to show a small but clinically significant benefit on the primary outcome because of the small number of patients

The European Trial of Free Light Chain Removal by Extended Hemodialysis in Cast Nephropathy (EuLITE) similarly randomized 90 patients with biopsy-proven cast nephropathy requiring dialysis to either conventional high-flux hemodialysis on the basis of clinical grounds (a minimum of 4-hour sessions thrice weekly) or extended high-cutoff hemodialysis (8-hour sessions on 8 of the first 10 days and then on alternate days) (C.C.P. Hutchison et al., unpublished data). All patients received bortezomib-based

chemotherapy. There was no difference in the primary end point of dialysis independence at 3 months between the control (51.6%) and intervention (55.8%) groups (relative risk, 1.07; 95% confidence interval, 0.73 to 1.59). Although there were large early reductions in serum free light-chain concentrations from pretreatment levels at days 4–6, there were no significant differences in median reduction rate of free light chains. There was a significant increase in the risk of pulmonary infections in the first 3 months in patients receiving high-cutoff hemodialysis (relative risk, 1.79; 95% confidence interval, 1.2 to 2.4; P,0.01). The rates of dialysis independence at 6 and 12 months were not reported. This study may have been underpowered to show a small but clinically significant benefit on the primary outcome because of the small number of patients. Because the EuLITE has only been published in abstract form, these findings should be interpreted cautiously until released in peer-reviewed fashion. It should be noted that there were several differences in the conduct of these two trials. The protocols differed in predialysis care, initial chemotherapeutic regimens, intensity of dialysis, and type of dialyzers used.

Despite the successful completion of these two trials, the role of high-cutoff hemodialysis in the treatment of cast nephropathy is still unsettled. Both studies failed to show an effect on the primary end point of dialysis independence at 3 months but may have bene underpowered to detect small but clinically significant benefit. Prolonged high-cutoff hemodialysis is not without risk. It is associated with a need for regular phosphate and albumin supplementation (the MYRE Trial) as well as a potential increase in infection risk (the EuLITE). Therefore, high-cutoff hemodialysis must still be considered an unproven adjunct therapy until more robust clinical data are reported, and it is likely unwarranted in non-dialysis-dependent AKI. Given the variable cytogenetics, type of free light chains, time course, and different medical treatment protocols associated with multiple myeloma, well designed trials of high-cutoff hemodialysis are still warranted in the future.

Disclosures. None.

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