The question of which of the CYP enzymes are responsible for formation of AAIa remains still to be investigated. The *in vitro* experiments of Xiao *et al.*[1] indicate that CYP1A generates AAIa. However, the model used to evaluate CYP1A participation in formation of AAIa *in vivo*, mice treated with an inducer of CYP1A 3-methycholanthrene (MC), did not bring unambiguous results. Namely, MC also induces other enzymes besides CYP1A. Although treatment of mice with MC leads to a decrease in AAI concentrations in the liver and kidney, an increase in AAIa concentrations was found not in the liver but only in the kidney of mice treated with the higher dose of AAI (20 mg/kg). An increase in excretion of AAIa due to its conjugation with glucuronide, caused by induction of UDP-glucuronosyltransferase with MC, could occur. Nevertheless, because CYP1A enzymes also activate AAI to species forming DNA adducts,[6] the decrease of AAI in liver and kidney might also result from this reaction. Moreover, NQO1, which is also efficiently induced by MC, could contribute to decreased AAI levels in MC-treated mice.

Taking into account all data known at the present time, we propose that the pathways of AAI metabolism are dictated by the binding affinity of AAI to CYP1A or NQO1, and their enzymatic turnover, as well as by the balance of the efficiency of CYP1A at oxidizing versus reducing AAI. In order to confirm this assumption and to complement the work of Xiao *et al.*,[1] we have started a study investigating formation of AAI-DNA adducts in the HRN mouse model and in models in which *CYP1A* genes are deleted.

Although the impact of individual enzymes that metabolize AAI on its nephrotoxicity and carcinogenicity *in vivo* is still not entirely resolved, one question was unambiguously answered by Xiao *et al.*:[1] hepatic CYP enzymes detoxicate AAI in mice, thus decreasing its renal toxicity. The evaluation of interindividual variations in the human enzymes playing a major role in AAI activation and detoxication, including their genetic polymorphisms, remains a major challenge to explain an individual's susceptibility to AAI and to predict cancer risk among AAN and BEN patients.

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Plasma exchange for myeloma kidney: cast(s) away?

WF Clark[1] and AX Garg[1,2]

Leung *et al.* (this issue) present a retrospective study of 40 patients. Observations in 14/40 led to the suggestion of restitution of plasma exchange for light-chain responsive, biopsy-proven myeloma kidney until a better randomized control trial (RCT) is constructed. A careful analysis of their study and a recent RCT suggest little difference in outcome between plasma exchange and control groups. The analysis supports restitution of a better RCT of plasma exchange for myeloma kidney rather than off-label use.

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Acute kidney injury in the setting of multiple myeloma has a strong impact on patient morbidity, mortality, health-care utilization, and cost.[1–4] A unique and important cause of acute kidney injury in multiple myeloma is cast nephropathy, in which renal inflammation results from an excess of filtered monoclonal light chains that are transported to the interstitium of the kidney via specific receptors in the proximal tubule. The receptors become overloaded by the light chains, which then combine with Tamm-Horsfall protein, forming obstructive casts in the renal tubules.[5] Plasma exchange has been shown to remove light chains transiently and may have an adjunctive effect when combined with effective chemotherapy in the treatment of cast nephropathy.[3,6,7]

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Two small randomized controlled trials (RCTs) of 29 and 21 patients provided conflicting results regarding the benefit of plasma exchange.[8,9] Recently, in a larger RCT, 97 patients presenting with myeloma and acute renal failure were randomized to receive standard chemotherapy with or without plasma exchange. This study failed to demonstrate a benefit of the addition of plasma exchange therapy.[10] Leung *et al.*[11] (this issue) now reconsider the role of plasma exchange in myeloma cast nephropathy in a retrospective case series. The series suffers from the usual shortcomings of a small retrospective analysis of a heterogeneous mixture of acute, subacute, and chronic renal failure patients with the diagnosis of myeloma (incident and recurrent cases) who receive a range of 1–19 plasma exchanges and 12 different chemotherapy protocols.

In this report, 40 cases are initially reported; 28 of these patients agreed to undergo renal biopsy, of whom 18 had cast nephropathy as a diagnosis. Of the 18, 14 had serum free-light chain measurement, and of these, 50% demonstrated a renal response to their plasma exchange therapy plus or minus other types of chemotherapy. In an exploratory uncorrected sub-sub-sub-subgroup analysis, nine patients had a greater than 50% reduction in serum free-light chains with a diagnosis of cast nephropathy, and seven demonstrated a renal response. A renal response was a composite outcome, which required the patient to be alive at 6 months and to have had a reduction in his or her baseline serum creatinine of 50% and to be independent of dialysis. Leung *et al.*[11] contend that their results are dependent on identification of patients with myeloma and renal failure who have cast nephropathy confirmed by renal biopsy and have serum free-light chain measurement. Unfortunately, only 14 of their 40 subjects met these requirements. This retrospective analysis noted no correlation between the number of plasma exchanges that patients received and their serum free-light chain response or their renal response. Although the subjects did receive 12 different types of chemotherapy, renal response did show a weak correlation with high-dose dexamethasone therapy. The renal response rates in the 18 patients with biopsy-proven cast nephropathy and the 14 patients with biopsy-proven cast nephropathy and serum free-light chain measurement are similar to the response rates noted for both control and plasma exchange subjects in the previous RCT (Table 1). The subjects in the previous RCT had incident myeloma, were followed prospectively, and had well-defined acute renal failure.[10] The expected incidence of cast nephropathy for this well-defined group would be anywhere between 77% and 100%.[1,2,4] Leung *et al.*[11] used a composite outcome that required that the patient be alive, have a 50% reduction in baseline serum creatinine, and dialysis independence at 6 months. The Clark *et al.*[10] outcome was death, dialysis dependence, or creatinine clearance less than 30 ml/min/1.73 m^2, and the inverse would be similar to the Leung *et al.*[11] outcome: life, dialysis independence, and serum creatinine improvement of 50% at 6 months from the time of diagnosis of acute renal failure (Table 1).

Table 1 demonstrates the comparative outcomes and shows that Leung *et al.*'s[11] plasma exchange group did not have a significantly different outcome from that of the control and plasma exchange arms of the Clark *et al.* RCT[10] (Table 1). However, the optimal outcomes noted for the sub-subgroup of cast nephropathy patients who responded with a 50% reduction in serum free-light chains after an unspecified number of plasma exchanges and differing chemotherapy appear superior to the RCT results. It is the outcome of this highly selected subgroup that has encouraged Leung *et al.*[11] to suggest restitution of plasma exchange therapy.

The increased benefit for the optimized patient group with biopsy and serum free-light chain reduction of 50% is more likely to be due to the type of chemotherapy and the responsiveness of the myeloma, rather than the plasma exchange therapy.[2,6,7] This is why the mortality rate among patients who received standardized chemotherapy in the Clark *et al.* study[10] did not differ between the plasma exchange and control arms, in contrast to the major difference between the response and the non-response group in the Leung *et al.* study.[11] The magnitude of survival advantage reported by Leung *et al.*[11] would be expected if a 50% reduction in serum free-light chain levels was merely a marker for patients whose myeloma was responsive to chemotherapy. Plasma exchange is not able to induce a lasting light chain response in the absence of chemotherapy in patients with myeloma.[6,7] The weak correlation noted by Leung *et al.*[11] for renal response to chemotherapy, coupled with the lack of association of the number of plasma exchanges with serum free-light chain response, is consistent with this interpretation.

Plasma exchange without chemotherapy is unlikely to exhibit clinical benefit in cast nephropathy because of free-light chain removal. Free-light chains are relatively small molecules (25–50 kilodaltons) and are present in similar concentration in the intravascular and extravascular compartments.[6] Thus about 15%–20% of free-light chains are available for removal, of which one volume plasma exchange would remove about 10%–15%. This would have little impact if chemotherapy did not reduce production. This has been clearly

Table 1 | Outcomes

Outcomes: 6 months	Composite renal response	Dialysis independence
Leung *et al.*[11]	18/40 = 45%	2/9 = 22%
	Myeloma, renal failure	PE
	9/18 = 50%	
	PE, CN	
	7/14 = 50%	
	PE, CN, sFLC	
Clark *et al.*[10]	13/26 = 50%	7/19 = 37%
	Control	Control
	21/38 = 55%	10/24 = 42%
	PE	PE

CN, cast nephropathy; PE, plasma exchange; sFLC, serum free light chains.

demonstrated in two recent publications that deal with the kinetics of free-light chain removal with the use of chemotherapy and plasma exchange.[6,7] We would contend that the 50% reduction in free-light chains noted by Leung *et al.*[11] marks those who responded to chemotherapy, as is suggested by the two recent publications and the recent RCT.[6,7,10]

Is it time to cast away plasma exchange forever as an ineffective method of improving renal and broader outcomes in patients with multiple myeloma? The answer is clearly no. As Leung *et al.*[11] highlight, the jury is still out, and there is no debate that better RCTs are needed to clarify the role of this therapy in multiple myeloma. However, is the American Society for Apheresis correct to describe plasma exchange as "having suggestion of benefit for which existing evidence is insufficient to establish the efficacy of benefit"? Our position is that the answer at this time is a clear yes. Our emphasis as a community should be to encourage patients to participate in future trials. There is a current RCT in the United Kingdom led by Dr. Gill Gaskin that commenced in 2004 and intends to enroll 280 patients with newly diagnosed multiple myeloma and acute kidney failure. Free-light chain measurement will be included, but renal biopsy is not an inclusion criterion in this well-constructed trial. We await this larger study with anticipation, but in view of the concerns of Leung *et al.*[11] about the need for renal biopsy, we would strongly encourage Leung *et al.* and those of similar interests to use both renal biopsy and serum free-light chain measurements in constructing the randomized control study that will test their hypothesis that plasma exchange improves renal outcomes in myeloma cast nephropathy. In the present environment it may be easier to recruit the numbers needed to carry out an RCT, as there will be less of the off-label use of plasma exchange that was noted in the previous RCT.[10] The RCT by Clark *et al.*[10] did suffer from the absence of renal biopsy and the measurement of serum free-light chain levels. However, we should not forget that the response rate with biopsy-proven cast nephropathy and measurement of free-light chains resulted in a similar 50% improvement in renal outcome for the cast nephropathy group of Leung *et al.*[11] and the control and plasma exchange arms of the Clark *et al.* RCT.[10]

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