

Plasma Exchange for Myeloma Kidney?

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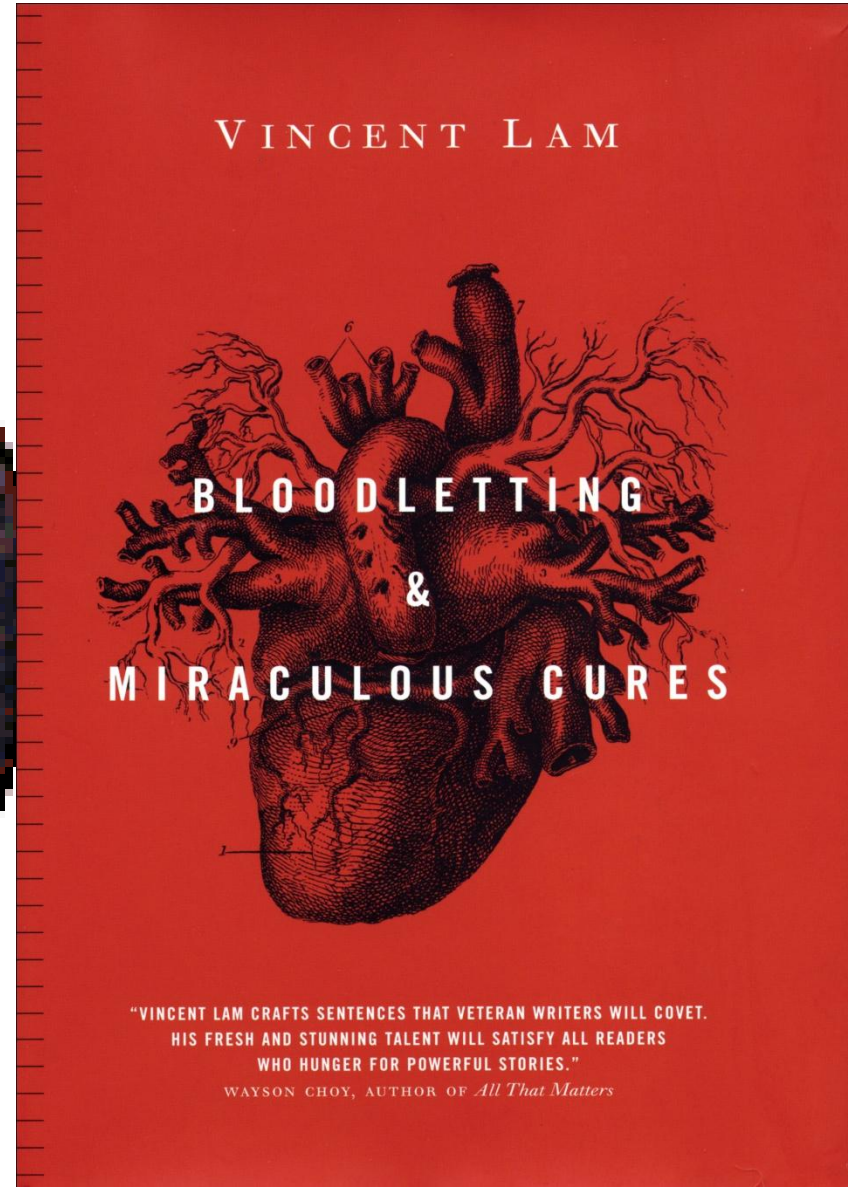
Scientist Lawson Health Research Institute



My Worst Nightmare being on the CON Side Against a Formidable Debater!



1) Mechanism: REMOVAL of the EVIL HUMOURS (Light Chains)



2) Retrospective observations of Leung et al KI 2008 most compelling

- “We performed this retrospective study to investigate the effectiveness of PLEX in the treatment of CN when the diagnosis is confirmed by renal biopsy and treatment is guided by serum-free light chain level”.
- 40 patients met inclusion criteria only 2/3 newly diagnosed myeloma and only 2/3 known duration of renal failure 28 underwent renal biopsy
- 18/40 (45%) that received PLEX achieved a renal response

Leung et al continued

- 18/28 recently and non recently diagnosed myeloma with renal biopsy had cast nephropathy and received 7 different immunosuppressive regimens
- Renal response to PLEX was reported in 50% of the 18 cast nephropathy and 14/18 reported a sFLC response to PLEX (no correlation with renal response and sFLC response)

Leung et al continued

- In a multivariate analysis of survival the only difference reported achieving statistical significance was newly diagnosed versus relapsed myeloma $p=0.004$ but not renal response $p=0.07$

Leung et al continued

- In a logistic regression model that adjusted for age ,sex and cast nephropathy renal response was predicted by either post treatment sFLC or 50%reduction of sFLC
- However no relationship was found between the number of PLEX and the post treatment sFLC levels($p=0.9$)

What does this mean?

- It suggests **chemotherapy response** not PLEX results in renal response
- 2) Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone containing regimens and impact of novel agents, E Kastritis et al Haematologica 2007
- 41 consecutive renal failure in newly diagnosed myeloma 15/ 41 dexamethasone high dose plus thalidomide or bortezomib >80% reversal of renal failure and in patients respond to therapy >85% reversal of renal failure without PLEX

FULL DISCLOSURE

- 3) I too was a believer following a retrospective analysis of our clinical experience with cohort comparison...but

3) Plasma Exchange in Rapidly progressive Renal Failure due to Multiple Myeloma L Moist, G Nesrallah, C Kortas, E Espiritu, T Ostby & WF Clark Amer J Neph 1999

- 16/24 did not require dialysis 13/14 alive at 1 year dialysis independent and 12/13 had a 25% reduction in creatinine at 3months
- “this retrospective study suggests that plasma exchange may offer some benefit in preventing the initiation or continuation of dialysis in patients with rapidly progressive renal failure secondary to multiple myeloma”

3) Plasma Exchange in Rapidly progressive Renal Failure due to Multiple Myeloma L Moist, G Nesrallah, C Kortas, E Espiritu, T Ostby & WF Clark Amer J Neph 1999

- “A randomized controlled prospective study is needed to determine whether plasma exchange should be recommended as a standard treatment for patients with rapidly progressive renal failure due to multiple myeloma”.

I am as guilty as most in wanting to treat my patients but...Evidence Not Observations set us apart from our noble predecessors the Barber Surgeons!



My Task is to Convince You!

One of These Things Is Not Like the Others ...



- 4) Zucchelli et al RCT KI 1988
- 4) Johnson et al Arch Intern Med 1990
- 5) Clark et al Ann Intern Med 2005

4) RCT by Zucchelli et al 1988

- 29 cases of ARF caused by old (10) or recently diagnosed MM (19)
- 17/29 renal biopsy
- Randomized to PLEX with Hemodialysis versus no PLEX with Peritoneal dialysis (testing 3 therapies in two arms with 29 subjects with a different prognosis)
- Study reported at 3 different time periods and enrolment numbers
- Final report in Kid Int 1 year mortality rate 34% versus 72% $p < 0.01$

4) Zucchelli et al

- 2 month mortality 7% versus 35%
- 6 mos to 1 year mortality most series in that time period <40% NOT 72%
- Best interpretation is **major baseline imbalance and small numbers** in study prevent randomization from providing an unbiased comparison of PLEX versus non PLEX
- What does this outcome mean? “13 of 15 patients in the treatment group recovered renal function reaching serum creatinine levels, ≤ 2.5 in **most** cases”

4) RCT by Johnson et al 1990

- 21 patients with MM with evidence of progressive renal failure
- 10 standard Rx 11 standard Rx plus PLEX
- Excluded 6 unresponsive to chemotherapy?
- No difference in creatinine or longterm dialysis 5vs4
- Conclusion: PLEX no effect : outcome dependent on severity of cast formation(biopsy interpretation)

Zucchelli and Johnson's Studies

- Small numbers unable to overcome baseline imbalances by randomization (hence major differences in mortality or biopsy severity)
- These studies are good attempts for their time period but do not remotely fulfill CONSORT Document Guidelines for reporting an RCT

5)Clark et al 2005

- 104 patients with recently diagnosed MM and onset of well documented ARF were randomized to standard therapy +PLEX versus standard therapy
- The two groups showed no difference in 14 known prognostic baseline variables at time of study entry

Hypothesis

- 5-7 plasma exchanges improves renal outcome in myeloma acute renal failure

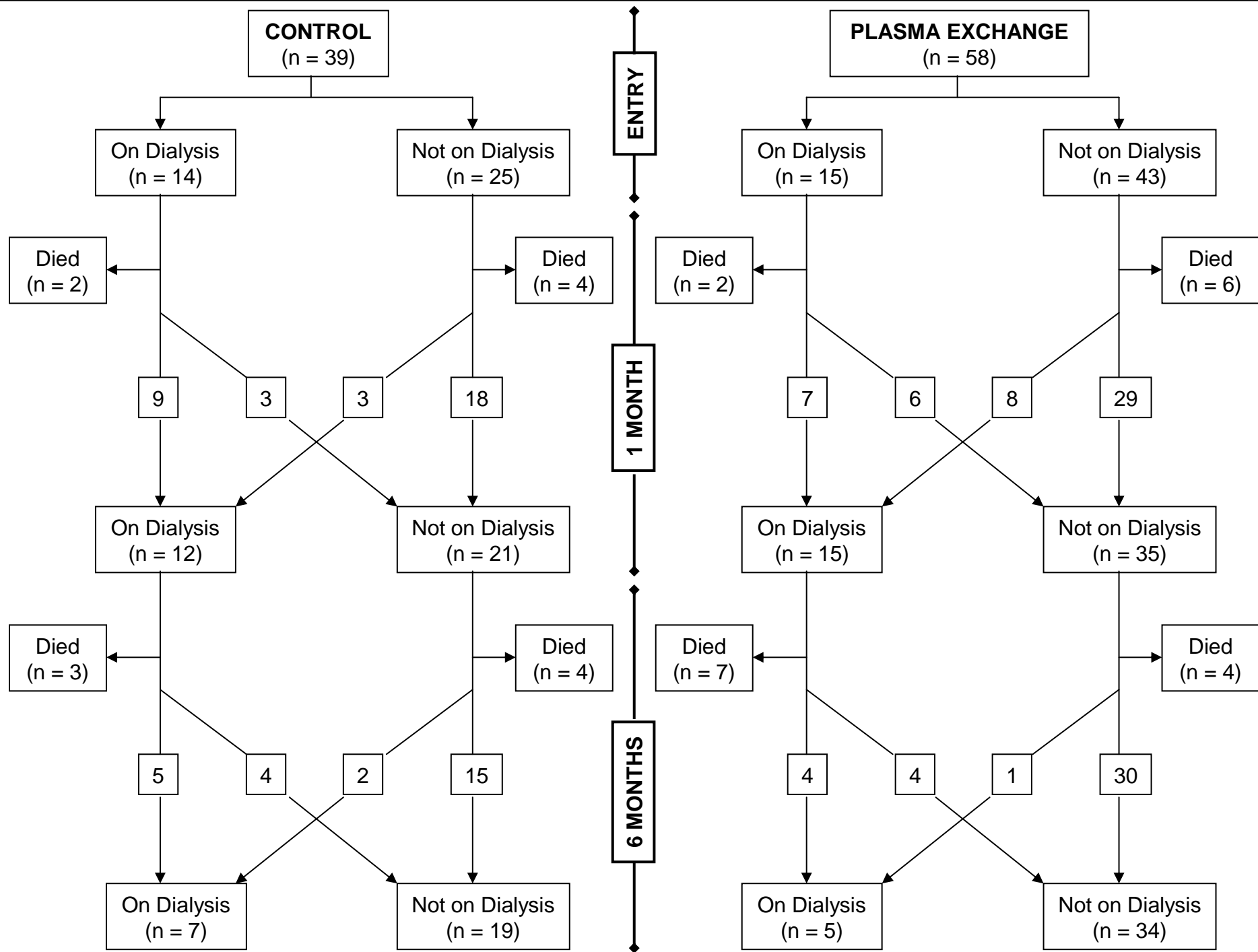
Primary Renal Outcome

Composite outcome – dialysis

dependence + death

+ creatinine clearance < 30 ml/min

@ 6 mos



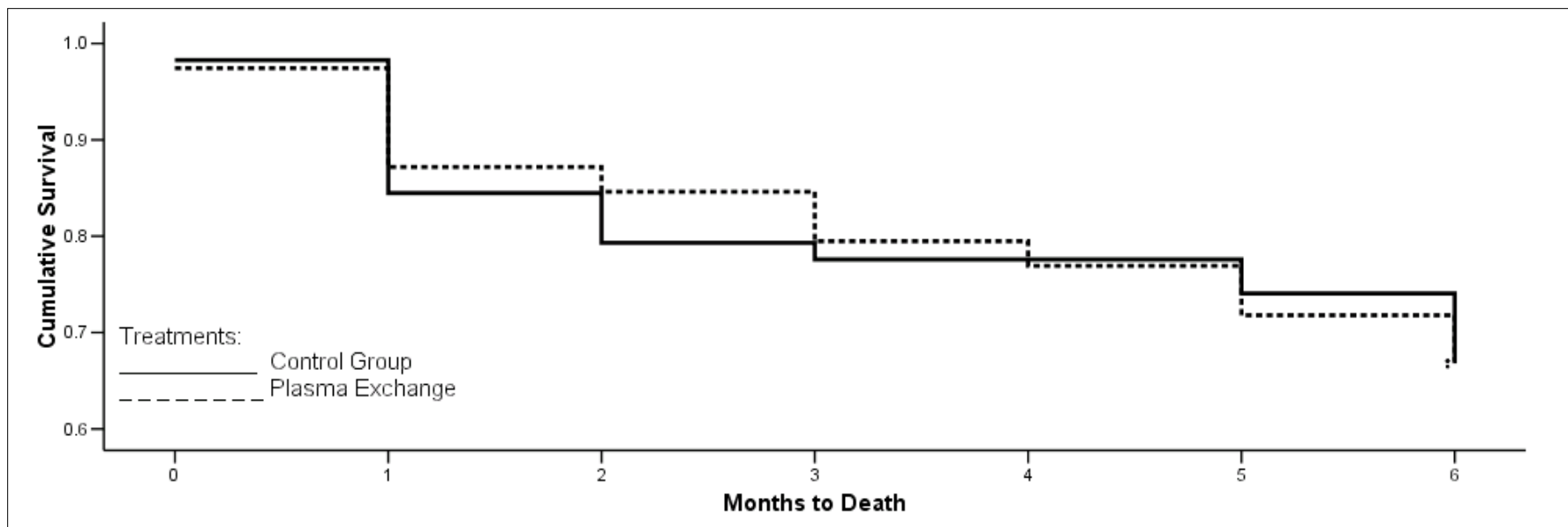


Figure 3: Kaplan-Meier Analysis of Time to Death. The median time to death in both groups was 6.0 months. Differences between them failed to achieve statistical significance by Log Rank comparisons for equality of survival distributions.

Conclusions

- 1) Primary Composite outcome occurred in 57.9% of PLEX and 69.2% of non PLEX difference 11.3% $p=0.36$
- 2) ARF at onset of Myeloma: no evidence for a substantial benefit in reducing **intention to treat primary outcome**: death, dialysis dependence or a MDRD GFR $< 30\text{ml}/\text{min}/1.73\text{m}^2$
- 3) This study satisfied reporting criteria for CONSORT Guidelines **NB intention to treat analysis**

Dr Leung will cleverly try to convince you:

- 1) Our study is irrelevant because we didn't routinely do renal biopsy in our patients and will quote incidence of cast nephropathy using a general autopsy series but...
- 2) Composite outcome using death not relevant yet all RCTs and his retrospective series measures mortality

BUT...

- 1) General autopsy series in myeloma -the kidney involved >50% whereas < 20% of patients presenting with myeloma have ARF

- 2) General autopsy series tells us about type of renal involvement over time (recent and remote cases) in all patients who die with diagnosis of multiple myeloma not those presenting with recent onset myeloma and **clinical picture of ARF** as noted in 4 specific series of **incident myeloma with ARF** where >93% compatible with cast nephropathy

Incidence of biopsy proven cast nephropathy in recent onset myeloma presenting with ARF

Case series	# of patients	Tumour 11B	Tumour 111B	Range S creatinine	Biopsy Myeloma Kidney
Rota et al 1987	34	15%	73%	164-2000	26/30
Pozzi et al 1987	50	12%	82%	273-1518	16/24
Pasquali et al 1990	25	24%	72%	455-1390	25/25
Irish et al 1997	56	22%	78%	302-2600	16/21
Total	165				83% another 10% CMK

CONCLUSIONS

- Dr Leung's report in KI of 2008 does raise an issue about plasma exchange's potential role in the treatment of light chain cast nephropathy.
- However we do differ with the author's interpretation that these 9 patients(sub, sub, sub analysis) justifies reinstatement of an unproven therapy.
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OUTCOMES

OUTCOMES	Renal Response	Independent of dialysis
<ul style="list-style-type: none"> Leung et al 	18/40=45% MM, renal failure 9/18 =50% PLEX &CN 7/14 =50% PLEX,CN,sFLC	2of 9 =22%
<ul style="list-style-type: none"> Clark et al 	13/26 No PLEX =50% 21/38 PLEX=55%	No PLEX 7 of 19=37% PLEX 10 of 24=42%
<ul style="list-style-type: none"> Kastritis et al 	12/15 No PLEX =80%	No PLEX 8/10=80%

CONCLUSIONS

WF Clark & AX Garg

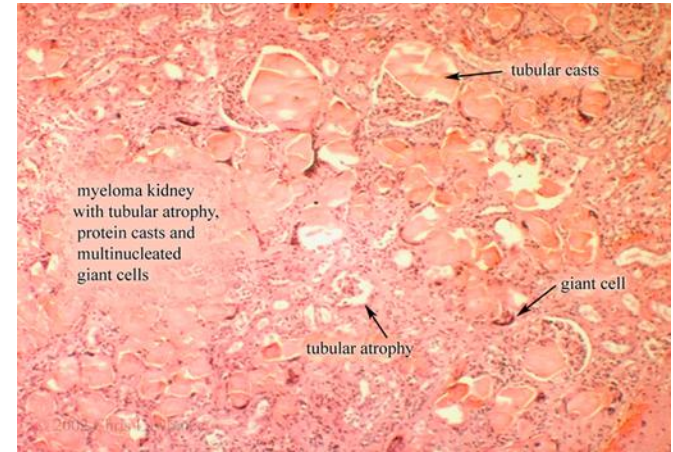
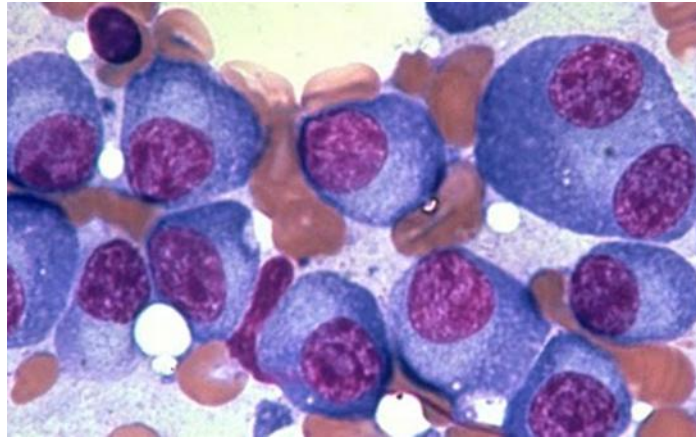
Kidney International Vol 73,1211-1213, 2008

- In light of our RCT“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 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.

CONCLUSIONS

WF Clark & AX Garg
Kidney International Vol 73,1211-1213, 2008

- However is the American Society of Apheresis correct to describe plasma exchange as "having suggestion of benefit for which existing evidence is insufficient to establish efficacy of benefit?"
- Our position is that the answer at this time is a clear **YES!**



PLEX for Myeloma Cast Nephropathy?

REBUTTAL: NO OR YES

I could say YES, Because



Letterman's Top Ten Reasons

- 10) PLEX patients do as well as non-PLEX patients
- 9) I like to treat people because I am a doctor
- 8) I have access to an apheresis machine
- 7) If I treat all comers and compare only those that respond to chemo, patients don't do worse than Clark's unPLEX controls
- 6) I would treat 1000 people if I could prevent 1 person going on dialysis
- 5) I believe it works so it works
- 4) in my personal experience it seems to work
- 3) I treat on the basis of my gut instincts and
- 2) It isn't harmful and it is inexpensive???
- 1) Based on the mechanism it should work

I would love to have an effective
therapy and I possess an
apheresis machine but I can't
rationalize because....

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The best evidence even with all the warts: Chemotherapy not PLEX!



Is the best explanation for my learned Colleague's results

From my PLEX Team to Yours



We want to thank you for your insightful comments and.....

- We strongly encourage you and your colleagues to construct the RCT which will test your hypothesis that plasma exchange improves renal outcomes in myeloma cast nephropathy using both renal biopsy and serum free light chain measurement in **INCIDENT** patients treated with thalidomide or Bortezomib plus high dose dexamethasone
- Until then we support ASFA Position









