Management of AKI in Myeloma: Novel Approaches

Dr Colin A Hutchison
Consultant Nephrologist, Hawke’s Bay DHB, NZ
Senior Lecturer, University of Birmingham, Birmingham, UK
Why are nephrologists interested in myeloma kidney?

- Myeloma accounts for about 2% of patients on ESRD programmes
- It feels as though it should be a fixable problem (AKI – often with limited fibrosis)
- Patients do…. badly
Severe Renal Failure and Myeloma – Oxford 1997

Figure 1. Survival for 54 patients with myeloma and renal disease.
Survival of patients with AKI and multiple myeloma

Figure 1. Survival for 54 patients with myeloma and renal disease.

Median survival 10.2 month

Figure 2. Survival of 107 patients with acute severe kidney injury and multiple myeloma.

Haynes et al NDT 2009
Chemotherapy: Improving myeloma outcomes (the Beaumont experience (Ireland))


Dialysis dependent

N-44

Murphy et al, BJH 2014
Chemotherapy: Improving myeloma outcomes *(the Beaumont experience (Ireland))*

All patients

N-262

Murphy et al, BJH 2014
AKI and myeloma

Key areas to improve patient outcomes:
1. Rapid diagnosis
2. New chemotherapy agents
3. Novel supportive strategies

Combined care
(Laboratory, Nephrology, Haematology)
Rapid diagnosis

Of myeloma causing AKI
((Free light chains))

Education to: ED teams
General Medicine
(hopefully less so Renal)
Freelite: A quantitative serum FLC assay
Assessment of 1877 patients with plasma cell dyscrasias

SPE and FLC only sensitivity:

- 100% of MM
- 99.5% of SMM
- 98% of AL amyloid
- 96% of Plasmacytoma
Serum free light chain measurement aids the diagnosis of myeloma in patients with severe renal failure.


142 patients with new dialysis dependent renal failure

41 with myeloma
Screening for MM in AKI

Unexplained AKI → Screen by serum FLC

- Clonal FLC ≥500 mg/l → Probable cast nephropathy → Consider renal biopsy
  Haematology-oncology work-up

- Clonal FLC <500 mg/l → No cast nephropathy
  → No monoclonal pathology

- Normal FLC ratio → No monoclonal pathology

Same day result

Cockwell P+ Hutchison CA Current Opinion in Nephrology and Hypertension 2010
Free light chain assays

Established polyclonal assays
(Freelite – The Binding Site)
Vs
New monoclonal assays
(Siemens)
Correlation of lambda assays

\[ R^2 \text{ Linear} = 0.302 \]
Management of myeloma kidney

Time to target FLCs??
Reductions in serum FLCs improves renal outcomes in myeloma kidney

Probability of renal recovery from cast nephropathy

For 80% of the population to have renal recovery there must be a 60% reduction in sFLCs

39 patients with cast nephropathy: Birmingham + Mayo

Management of myeloma kidney: reducing FLCs

How do we reduce serum FLC levels?

Two components:

- Effective chemotherapy – novel agents
- Direct removal of FLCs from the serum
## Dose modification in renal impairment

<table>
<thead>
<tr>
<th></th>
<th>Degree of renal impairment</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thalidomide</strong></td>
<td>Any</td>
<td>Not required</td>
</tr>
<tr>
<td><strong>Lenalidomide</strong></td>
<td>Mild RI (CrCl 50-80mL/min)</td>
<td>25mg (full dose) every 24 hours</td>
</tr>
<tr>
<td></td>
<td>Moderate RI (CrCl 30-49mL/min)</td>
<td>10mg every 24 hours</td>
</tr>
<tr>
<td></td>
<td>Severe RI (CrCl &lt;30mL/min)</td>
<td>15mg every 48 hours</td>
</tr>
<tr>
<td></td>
<td>Severe RI (requiring dialysis)</td>
<td>15mg three times per week</td>
</tr>
<tr>
<td><strong>Bortezomib</strong></td>
<td>Any</td>
<td>Not required</td>
</tr>
</tbody>
</table>

RI – renal impairment; CrCl – creatinine clearance.
Novel agents: Bortezomib

Attractions to use in severe AKI / MM:

• Not renal excreted
  – Liver
  – No need to dose reduce

• Highly protein bound – limited dialysis removal

• Acts within 1 hr – 72hrs

• Myeloma response rapid (2-3 cycles)
Light Chain–Induced Acute Renal Failure Can Be Reversed by Bortezomib-Doxorubicin-Dexamethasone in Multiple Myeloma: Results of a Phase II Study

Heinz Ludwig, Zdenek Adam, Roman Hajek, Richard Greil, Elena Tóthová, Felix Keil, Eva Maria Autzinger, Josef Thaler, Heinz Gisslinger, Alois Lang, Miklós Egyed, Irene Womastek, and Niklas Zojer

- 68 patients with MM and AKI (GFR<50)
- Treated with Bortezomib, Dexamethasone and Doxorubicin
- Tumor response in 84% of patients

- Renal response in 62%
- Only 3 of 9 dialysis dependent patients recovered renal function
Reversibility of Renal Impairment in Patients With Multiple Myeloma Treated With Bortezomib-Based Regimens: Identification of Predictive Factors

Meletios A. Dimopoulos, Maria Roussou, Maria Gavriatopoulou, Flora Zagouri, Magdalini Migkou, Charis Matsouka, Despina Barbarousi, Dimitrios Christoulas, Erasmia Primenou, Irini Grapsa, Evangelos Terpos, Efstathios Kastritis

- Cohort of patients with renal impairment and MM
- Treated with Bortezomib and Dexamethasone
- 59% of patients had a degree of renal recovery
- Median time to renal recovery – 11 days
- Only 2 of 9 dialysis dependent patients had renal recovery
Management of myeloma kidney: reducing FLCs

Is chemotherapy alone enough??
Management of myeloma kidney: reducing FLCs

How do we reduce serum FLC levels?

Two components:

- Effective chemotherapy – novel agents
- Direct removal of FLCs from the serum
Why remove FLCs - kinetics in renal failure

As kidneys fail serum half-lives increase

Hutchison et al, cJASN 2008
Why remove FLCs - kinetics in renal failure

As kidneys fail serum half-lives increase

Both: P<0.01

Hutchison et al, cJASN 2008
Why remove FLCs - kinetics in renal failure

As kidneys fail serum half-lives increase

Both: P<0.01

Hutchison et al, cJASN 2008
Direct removal of FLCs from the serum: Plasma exchange – a logical treatment
Renal Improvement in Myeloma with Bortezomib plus Plasma Exchange

- 14 patients
- 7 new presentation
- Median 8 Plex
- 86% partial renal response

Brian L. Burnette, M.D.
Nelson Leung, M.D.
S. Vincent Rajkumar, M.D.
Mayo Clinic
Rochester, MN
rajkumar.vincent@mayo.edu
Largest RCT of plasma exchange: no renal benefit, no survival benefit

Clark
Ann I Med 2005
Why does plasma exchange not work??

**Mathematical model:**
- Two compartment model to evaluate the kinetics (movement) of FLCs in patients with MM and AKI

**Plasma exchange:**
- Effectively clears the intra-vascular volume
- But short duration therapy
- Therefore extra-vascular compartment is not cleared
- FLCs are 80% extra-vascular
- Therefore total body load of FLCs is not significantly reduced
Extended removal of FLCs from the serum is required:

Extended treatment will allow:
Extra-vascular FLCs $\rightarrow$ Intra-vascular $\rightarrow$ Removed

**Haemodialysis:**
- Safely undertaken over extended periods of time
- Unsuccessful with conventional dialysers because of the small pore size
- *In-vitro* we assessed FLC removal by ‘super-flux’ dialysers
- Only the Gambro HCO 1100 could effectively remove monoclonal FLCs
Pore Sizes of High Cut-Off (HCO) Membranes in comparison to HighFlux and plasmafiltration membranes

Courtesy of Dr Storr, Hechingen, Germany
HCO Membrane

Increased permeability for middle molecules

Convective permeability
Gambro HCO 1100 – 6 hour dialysis

Hutchison et al. JASN March 2007
Pilot Study of FLC removal by HCO-HD

**Aim:** Evaluate the removal of FLCs by extended HD in patients with biopsy proven cast nephropathy + dialysis dependent acute renal failure

**Combination of chemotherapy and HCO-HD:**

- Chemotherapy: high dose dexamethasone and thalidomide for *de novo*; bortezomib for relapsing
- Daily extended (8 hours) HD using the Gambro HCO 1100 – 5 days
- HD then reduced to alternate days for next 21 days or until FLC concentrations <500mg/L

*Hutchison et al. cJASN 2009*
Primary outcome: FLC reductions

6 Patients
Chemotherapy stopped

13 Patients continuous combined HD and chemotherapy

P<0.01

Hutchison et al cJASN 2009
Recovery of renal function

14 of 19 patients

Hutchison et al cJASN 2009
Renal recovery rates in study population and a case matched control population

Hutchison et al, EDTA 2008.
Study population’s survival relates to recovery of renal function

Hutchison et al, EDTA 2008.
International experience with HCO-HD Chart Audit of Renal Recovery in Multiple Myeloma – HCO 1100

- 67 patients treated across Europe and Australia
- Median 12 sessions
- 63% had renal recovery
Benefit of FLC removal in relation to degree of renal impairment

<table>
<thead>
<tr>
<th>Residual renal function (ml/min/1.73m²)</th>
<th>FLC exposure (g/day)</th>
<th>Additional reduction achieved with FLC removal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>without FLC removal</td>
<td>with FLC removal</td>
</tr>
<tr>
<td>0</td>
<td>418</td>
<td>117</td>
</tr>
<tr>
<td>3</td>
<td>314</td>
<td>106</td>
</tr>
<tr>
<td>6</td>
<td>251</td>
<td>97</td>
</tr>
<tr>
<td>15</td>
<td>157</td>
<td>77</td>
</tr>
<tr>
<td>24</td>
<td>114</td>
<td>64</td>
</tr>
</tbody>
</table>

ANZSN Oral Mini-Poster Session 2012
Study protocol

**European trial of free light chain removal by extended haemodialysis in cast nephropathy (EuLITE): A randomised control trial**

Colin A Hutchison*¹,², Mark Cook³, Nils Heyne⁴, Katja Weisel⁵, Lucinda Billingham⁶, Arthur Bradwell⁷ and Paul Cockwell¹,²

**Hypothesis**

The EuLITE trial examines the hypothesis that FLC removal haemodialysis will increase the rate of renal recovery in patients with cast nephropathy, severe renal failure and *de novo* multiple myeloma.
Randomised and controlled

90 Patients recruited

Randomisation

Control Arm HD
45 Patients
Standard high-flux HD

Research Arm HD
45 Patients
Extended HD on HCO 1100

‘Modified PAD regimen’ Chemotherapy

(P) VELCADE™ (bortezomib) iv 1.0 mg/m²
(A) Adriamycin (Doxorubicin) iv 9.0 mg/m²
(D) Dexamethasone oral 40 mg

primary outcome = independence of dialysis at 3 months
- 15 UK centres
- 4 German centres
MYRE – A French RCT

How to manage renal impairment in MM:

Part 1 – Moderate renal impairment and new MM:
• 200 patients randomized to CBD or BD

Part 2 – Severe renal impairment and new MM:
• 90 patients with biopsy proven myeloma kidney randomized to FLC removal HD or standard care
If EuLITE/MYRE return positive results – who should be treated?

- MM patients with severe renal failure
- Cast nephropathy
- High serum FLC levels
- Suitable for chemotherapy
Multiple Myeloma: Light chain kinetics and recovery from dialysis

Serum lambda (mg/L) vs. Days

- Dexamethasone
- Bortezomib
Combined Care in Myeloma Kidney - Summary

1. Rapid diagnosis is essential - Freelite

2. Early initiation of disease specific treatment
   1. High dose dexamethasone
   2. Bortezomib

3. In severe kidney failure – direct removal of FLCs may be indicated
   1. EuLITE – 2013
   2. MYRE – 2013/14
International Kidney and Monoclonal Gammopathy Research Group (IKMG*)

The IKMG unites physicians worldwide to help patients with light chain-associated kidney diseases
Evolving Strategies in the Diagnosis, Treatment, and Monitoring of Myeloma Kidney

Colin Hutchison, MD
Paul Sanders, MD
Guest Editors
Acknowledgements

EuLITE Investigators

IKMG members

University Hospital Birmingham:
  – Dr Paul Cockwell
  – Dr Mark Cook

University of Birmingham:
  – Prof A.R. Bradwell

The University of Tubingen:
  – Dr Nils Heyne

The Mayo Clinic:
  - Dr Nelson Leung

Grant 05-007