Challenging Cases in Hematology / Oncology
"How I Treat Newly Diagnosed Multiple Myeloma with Acute Kidney Injury"

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Multiple Myeloma in 15 minutes or less…..

- Case Presentation
- Pathophysiology of AKI in MM
- Treatment of AKI in NDMM
  - Light chain removal
  - Disease directed therapy
- Case follow up
- Q&A

55 year old man….

- 55 year old, Hispanic man presents with worsening back pain during physical therapy
- Routine plain films identify lytic bone lesions throughout the lumbar spine, oncology referral made
  - Hemoglobin 13.4; creatinine 1.0
- 2 months later patient establishes with oncologist
  - Labs and bone marrow biopsy ordered
- Bone marrow biopsy performed 10 days later
  - Marrow hypercellular with 70% plasma cells
  - Hgb 10.7; creatinine 4.7
  - sFLC: 6,824.6; lambda 6.8; K:L 1,008
  - M-spike: 0.7, IFE: IgGK

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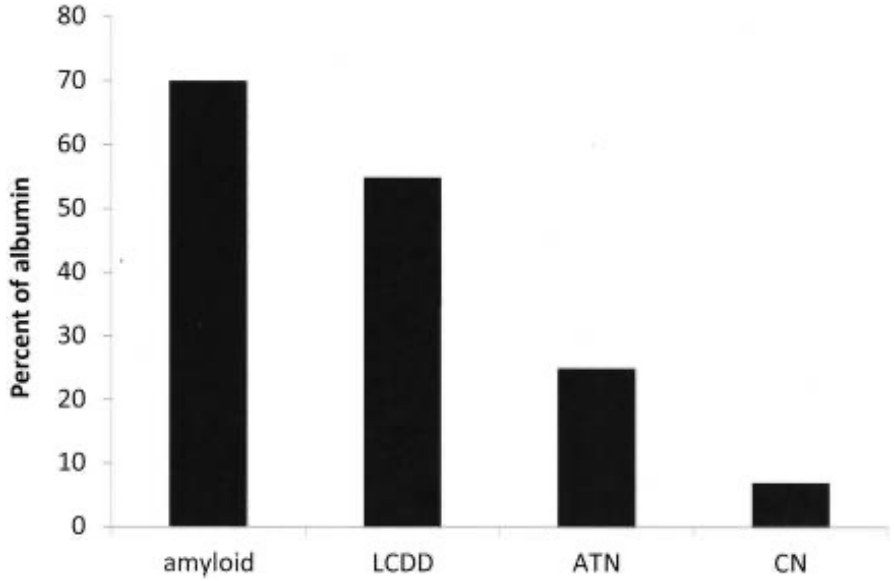
Acute Kidney Injury in NDMM

- IMWG definition: creatinine > 2 or eGFR </= 40 related to MM
- 15-20% of patients will present with AKI depending on definition
- Classic myeloma kidney is due to light chain casts that precipitate with uromodulin
- 15% of renal insufficiency in NDMM is unrelated or driven by protein deposition (Amyloid, acute tubular necrosis, light chain deposition)
- Diagnosis is tricky: can rely on 24 hour urine protein electrophoresis
  - Excretion of light chains only suggests cast nephropathy
  - Albuminuria suggests another cause



Dimopoulos et al JCO 2015, Finkel et al CJASN 2016, Nasr et al AJKD 2012

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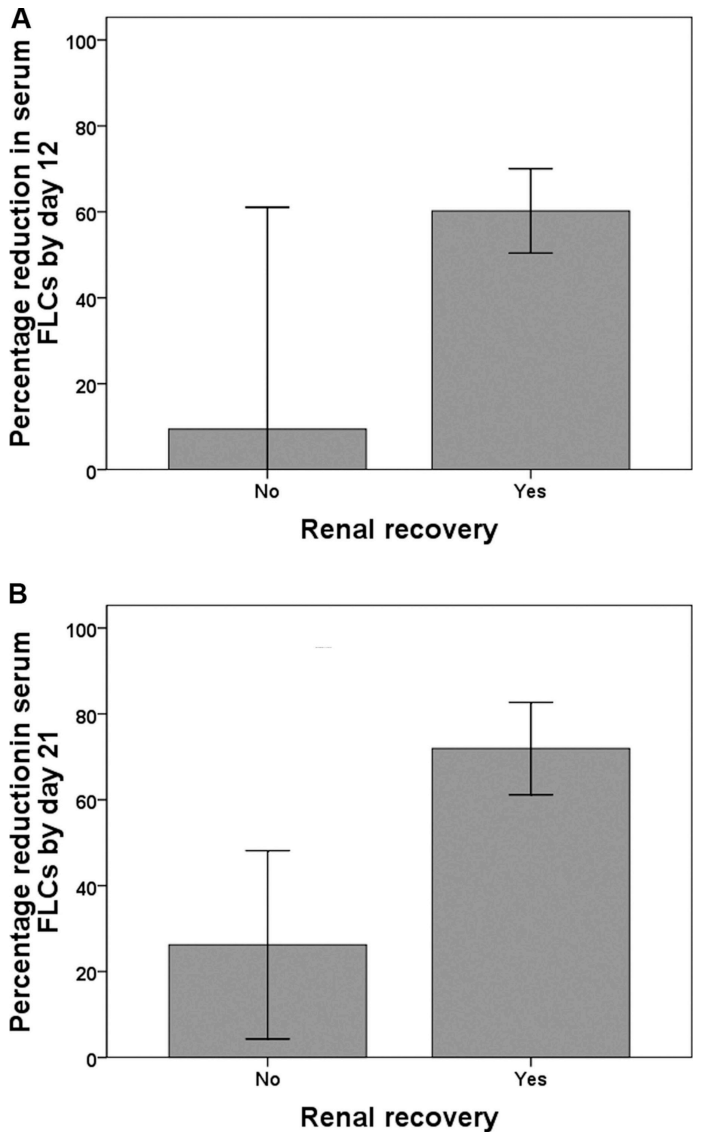
Reversing Cast Nephropathy in NDMM

- This is an urgency/emergency
- Clear light chains from tubules
  - Hydration
  - Bicarbonate is unproven
    - AVOID in hypercalcemia
- Decrease light chain production
  - Again, time is of the essence



Hutchinson et al JASN 2011

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Getting rid of light chains

- Plasma Exchange
  - Theoretical benefit for cast nephropathy
  - However, light chains are total-body volume distributed – even when all plasma exchanged, there is rapid rebound of light chains
  - Expensive, and with risk (exposure to donor plasma, line placement etc)
  - Only 1 RCT available (did NOT confirm cast nephropathy)

Receiving dialysis or GFR < 0.29 mL · s^{-2} · m^{-2} (<30 mL/min per 1.73 m^2) at 6 mo‡		
Received plasma exchange	2.083 (0.758–5.727)	0.890 (0.221–3.583)
Received VAD chemotherapy	0.850 (0.318–2.272)	0.474 (0.093–2.410)
Receiving dialysis at baseline	0.579 (0.197–1.700)	0.300 (0.058–1.544)
Durie–Salmon stage IIIB	0.864 (0.307–2.432)	0.968 (0.228–4.120)
Age at entry	0.987 (0.946–1.029)	0.940 (0.876–1.008)
Baseline urine protein level	0.967 (0.908–1.030)	0.940 (0.852–1.036)
Baseline serum albumin level	0.895 (0.830–0.965)	0.873 (0.786–0.968)

Finkel et al CASJN 2016, Clark et al Ann Int Med 2005

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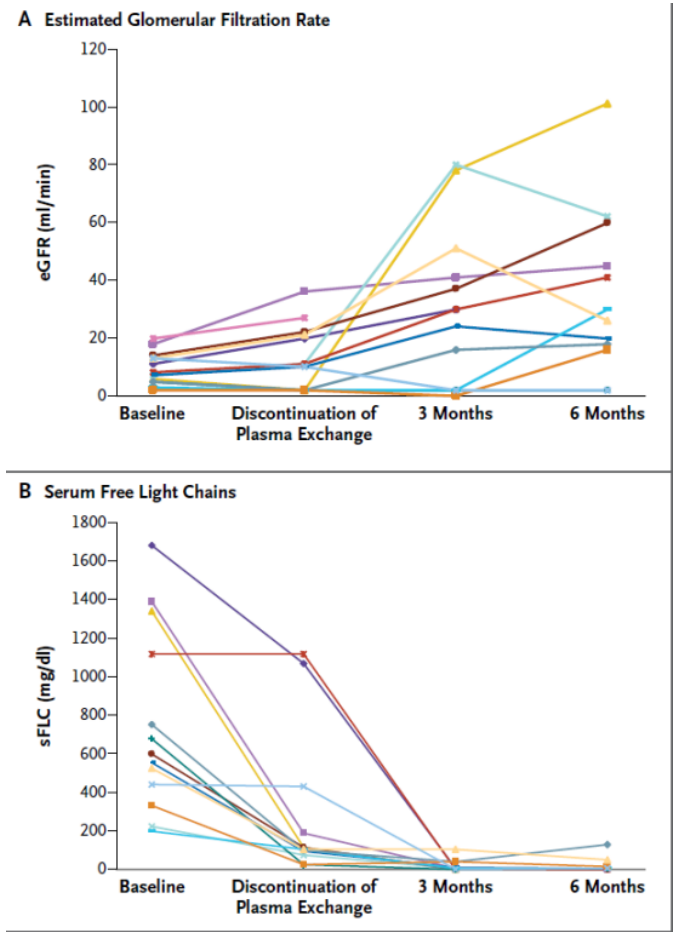
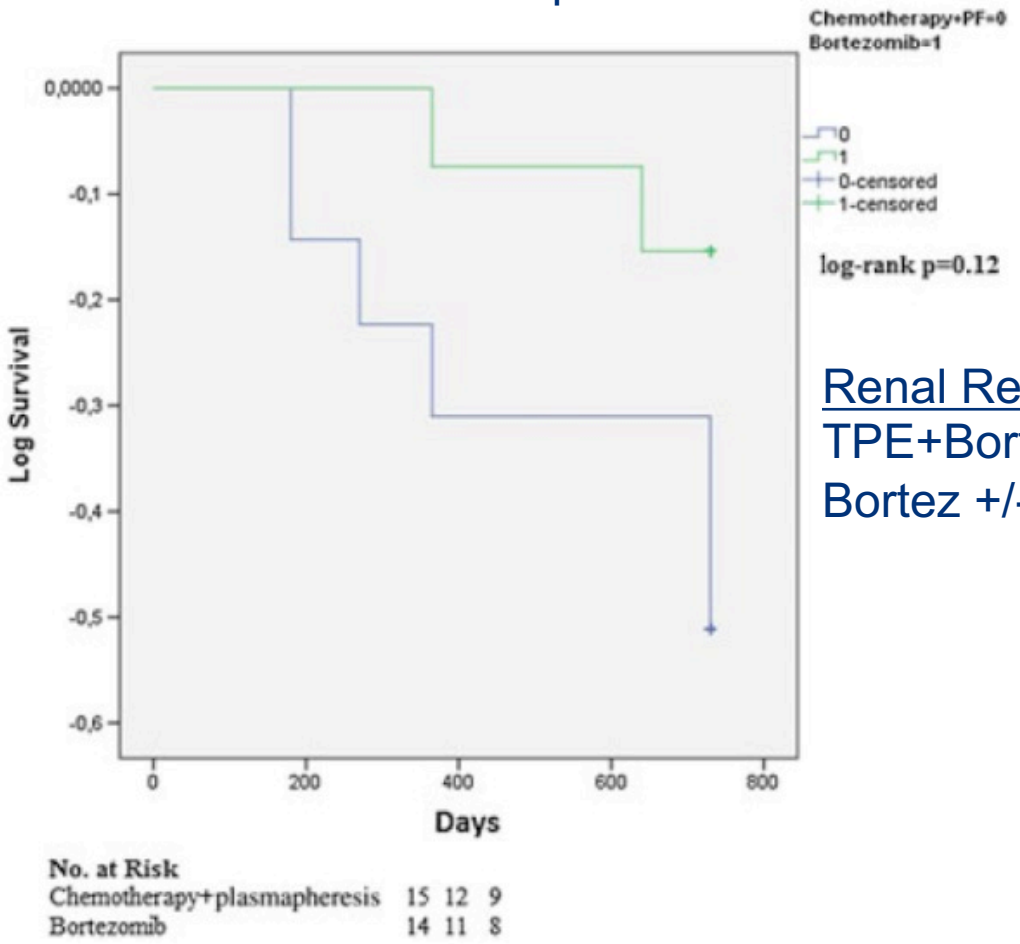
Plasma Exchange + Bortezomib based therapy



Overall Survival of AKI patients with NDMM



Renal Recovery rates:
TPE+Bortez+Chemo: 87%
Bortez +/- Chemo: 86%

Burnette et al NEJM 2011, Premuzic Ther Apher Dial 2018

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Should we still be considering Plasma Exchange?

- Generally no – some small retrospective series imply benefit, others do not
- HOWEVER – the entrance criteria to both prospective AND retrospective studies have done a poor job at isolating the patients most likely to benefit from plasma exchange
- In patients with minimal albuminuria, high clonal light chains on 24 hour urine and progressive AKI, one should consider it

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A Quick Word on High-Cutoff Hemodialysis

- High-Cutoff hemodialysis (HCO-HD) uses a permeable filter in HD patients that can rapidly clear light chains
- Theoretical benefits over plasma exchange:
  - Can have longer treatments than plasma exchange (clear more light chains)
  - No exposure to exogenous plasma

Bridoux et al, JAMA 2017, Hutchison et al, Lancet Haem 2019

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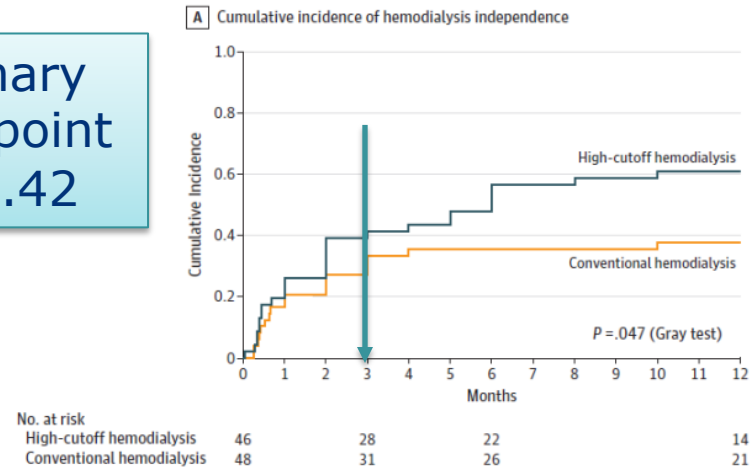
Does HCO-HD Work?

Primary Endpoint p=0.42

Figure 2. Kidney and Patient Outcomes



MYRE study:
- All patients with NDMM
- biopsy proven cast nephropathy
- those requiring HD randomized to HCO vs standard HD
- All received bortez-dex; hematologic non-responders received cyclophosphamide 750 mg/m2 q21days

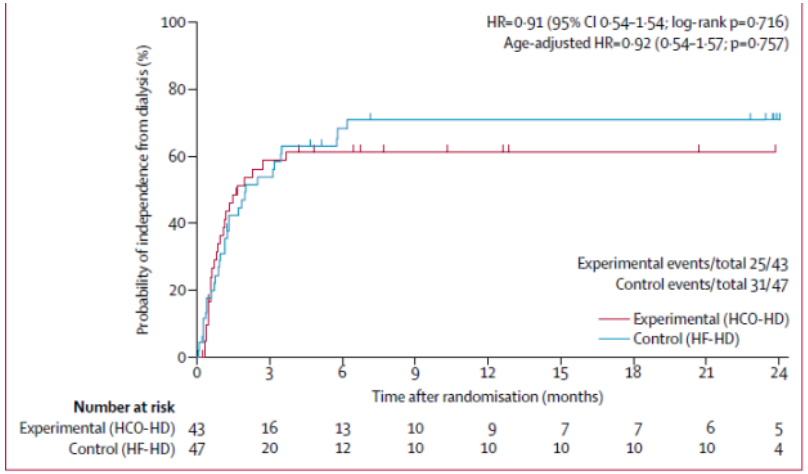


Figure 3: Reverse Kaplan-Meier graph of time to independence from dialysis by treatment group
HCO-HD=high cutoff haemodialysis. HF-HD=high-flux haemodialysis. HR=hazard ratio.

EuLITE Study:
- All patients with NDMM
- Biopsy proven cast nephropathy
- Dialysis dependent
- Randomized to HCO vs standard HD
- All patients received bortezomib, doxorubicin, dex (PAD)

Bridoux et al, JAMA 2017, Hutchison et al, Lancet Haem 2019

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Summary Thus Far

- Acute kidney damage in NDMM is multifaceted
- Supportive measures aimed to decreasing toxic effects of light chains, hypercalcemia, dehydration
- Myeloma Kidney (Cast Nephropathy) requires clearance of light chains to recover
  - Plasma exchange MAY be useful
  - High Cutoff HD Not readily available (we don't have it at UCD)
  - Conflicting results from two well designed RCTs
    - Differences in MM therapy or response rates may have made a difference
    - Differences in disease response
    - MYRE 3 month ≥VGPR rates: 61% HCO vs 44% HD
    - EuLITE 6 month ≥VGPR rates: 37% HCO vs 62% HD
- Rapid Response to treatment is necessary for renal recovery

How do we achieve a rapid renal response

- Bortezomib based regimens
  - Not nephrotoxic
  - Can lead to rapid reduction in light chains
- Dexamethasone
- Is a third agent needed?
  - Note differences in MYRE vs EuLITE study in dialysis independence

Randomized Trial Comparing Double Versus Triple Bortezomib-Based Regimen in Patients With Multiple Myeloma and Acute Kidney Injury Due to Cast Nephropathy

Frank Bridoux, MD, PhD[1,2,3]; Bertrand Arnulf, MD, PhD[4]; Lionel Karlin, MD[5]; Nicolas Blin, MD[6]; Nolwenn Rabot, MD[7]; Margaret Macro, MD[8]; Vincent Audard, MD, PhD[9]; Karim Belhadj, MD[10]; Brigitte Pegourie, MD[11]; Pierre Gobert, MD[12]; Emilie Cornec Le Gall, MD, PhD[13]; Bertrand Joly, MD[14]; Alexandre Karras, MD, PhD[15]; Arnaud Jaccard, MD, PhD[2,3,16]; Karine Augeul-Meunier, MD[17]; Salomon Manier, MD, PhD[18]; Bruno Royer, MD[19]; Denis Caillot, MD, PhD[20]; Mourad Tiab, MD[21]; Sébastien Delbes, MD[22]; Felipe Suarez, MD, PhD[23]; Cécile Vigneau, MD, PhD[24]; Sophie Caillard, MD, PhD[25]; Nina Arakelyan-Laboure, MD[26]; Damien Roos-Weil, MD, PhD[27]; Sylvie Chevret, MD, PhD[28]; and Jean Paul Fermand, MD[4]; for the MYRE study group

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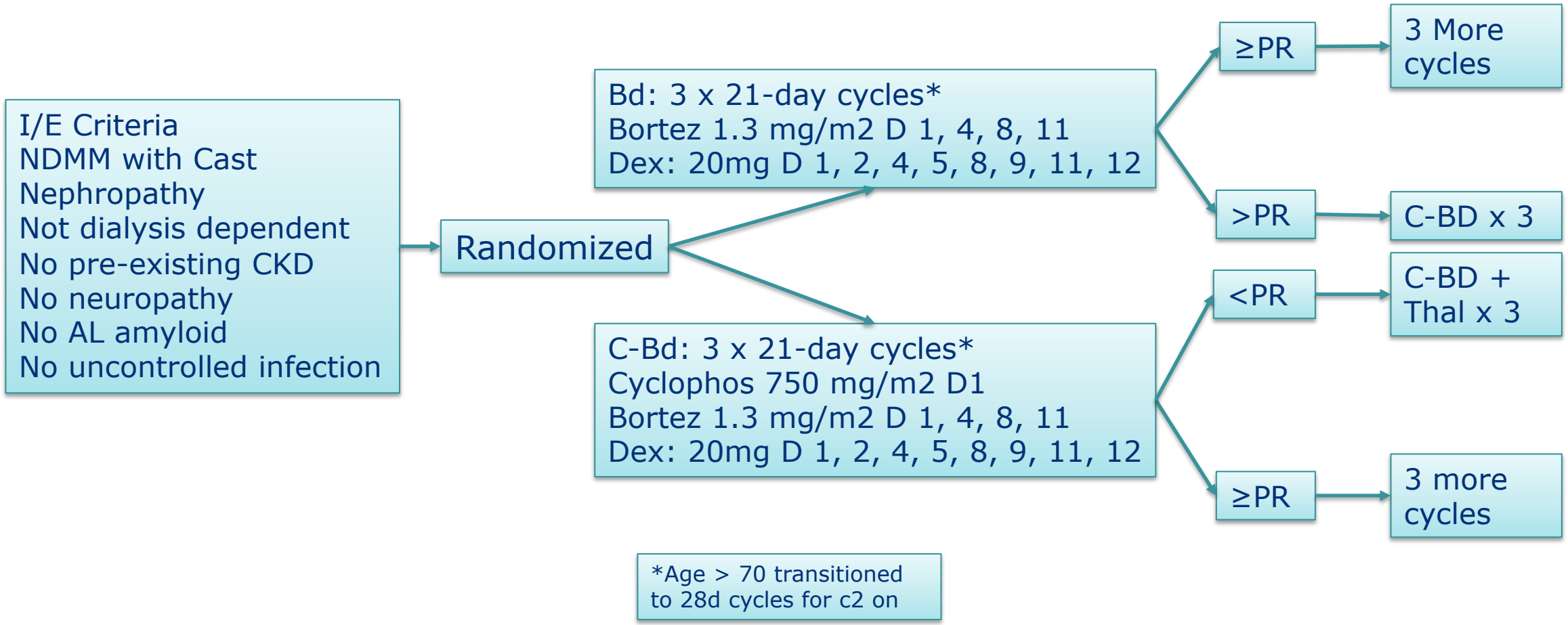
MYRE: Study Design (Non HD component)



Bridoux et al JCO 2020

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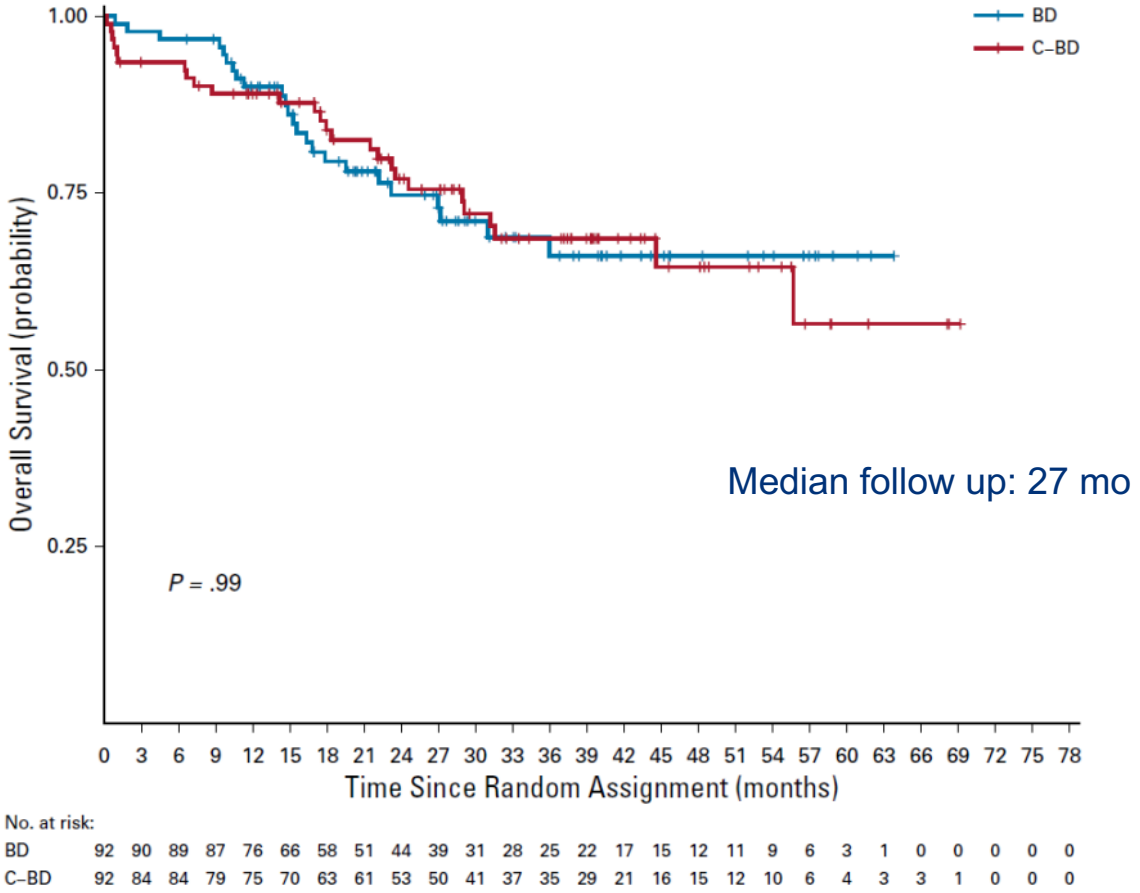
Results

- Renal response at 3 months
  - BD: 44.6%
  - C-BD: 51.1%
  - Risk ratio 0.87 (0.64 – 1.18)
- Overall Response at 3 months
  - BD: 78.3%
  - C-BD: 77.2%
- ≥VGPR at 6 months
  - BD: 46.8%
  - C-BD51.1%
  - RR 0.88 (0.66 – 1.17)



Bridoux et al JCO 2020

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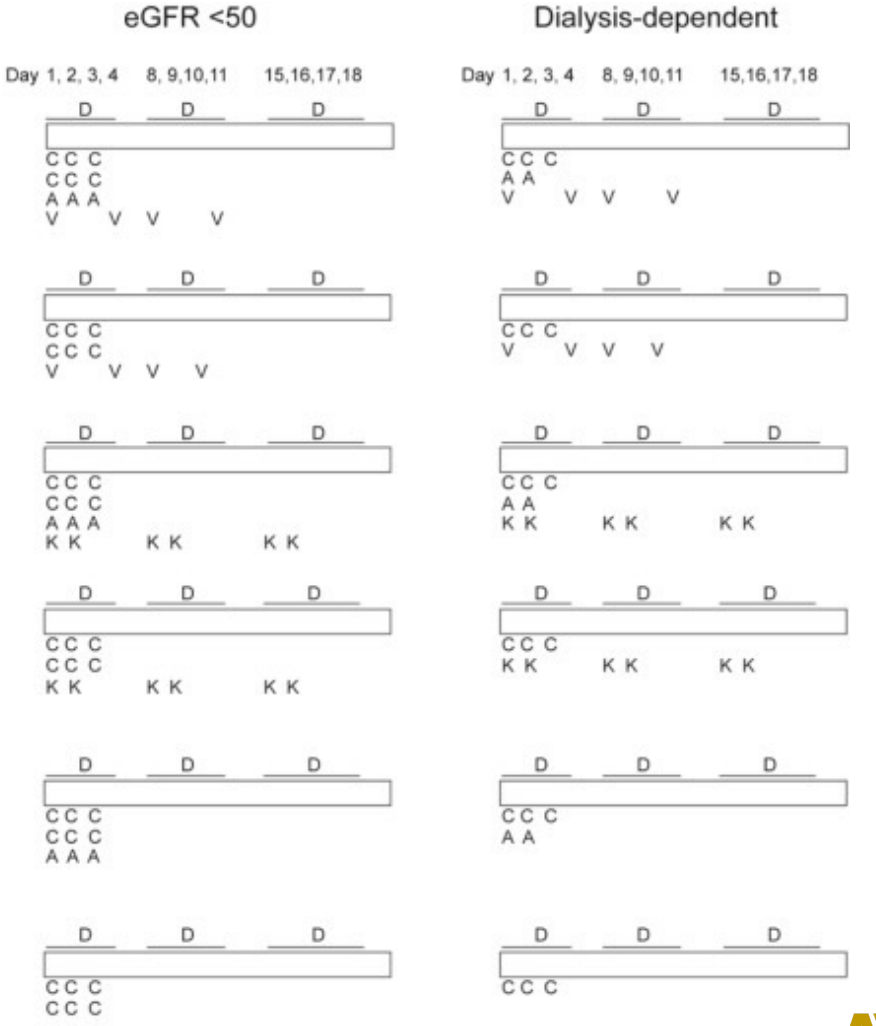
Modified HyperCAD

- Cy 350 mg/m2 BID, Dex 40 mg pulsed, +/- doxorubicin, +/- PI
- NDMM: 12 patients
  - 25% eGFR <50
- RRMM / intensification: 119
  - 30% eGFR <50



Narayan et al, CLML 2020

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Results in patients with AKI

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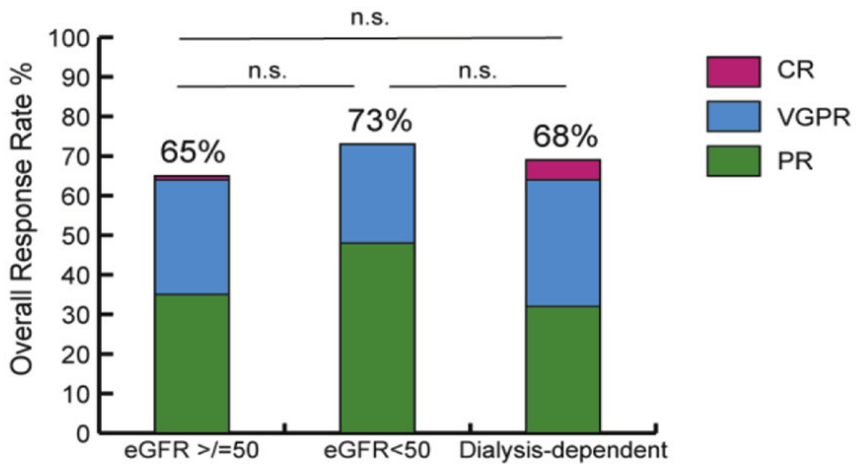

ORR	47 (65.3)	29 (72.5)	13 (68.4)
CR	1 (1.4)	0 (0.0)	1 (5.3)
VGPR	21 (29.2)	10 (25.0)	6 (31.6)
PR	25 (34.7)	19 (47.5)	6 (31.6)

Toxicity	
Neutropenic Fever	24%
Infection	37%
Cardiac Events (consistent across dosing schemes)	15%

Renal Responses (defined as improvement in serum creatinine): 80%
Worsening renal function: 20%

Narayan et al, CLML 2020

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mCBAD

- Cyclophosphamide 350 mg/m2 BID d1-4
- Bortezomib 1.3 mg/m2 d 1, 4, 8, 11
- Doxorubicin 9 mg/m2 CIV d1-4
- Dex 40 mg pulse

- NDMM n=13, RRMM n=116
- AKI
  - NDMM: 69%
  - RRMM: 31%

Tabchi et al CLML 2019

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mCBAD

- Overall response in NDMM 100%
  - ≥VGPR 46%
  - 85% had 1-2 cycles only
- Renal response NOT reported

Toxicity	
Neutropenic Fever	26%
Infection	37%
Neuropathy	24%
CHF/arrhythmia	3%

Tabchi et al CLML 2019

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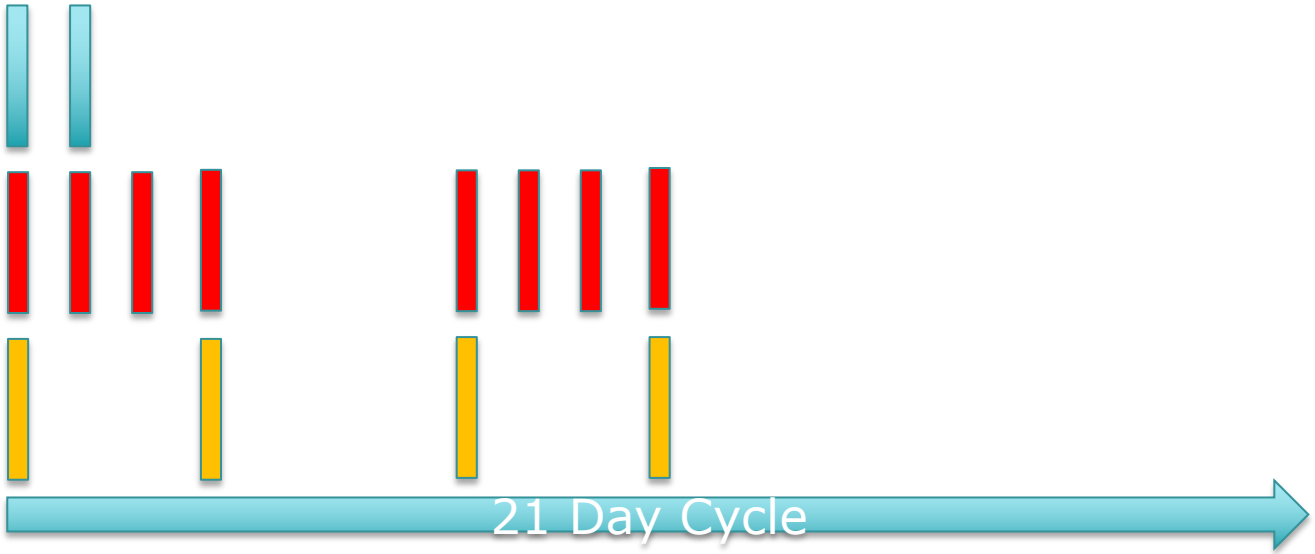
The UCD approach: Intensified CyBorD

- Based on potential cardiotoxicity of Hyper CD/CAD/CVD we have opted for fractionated cy at lower dose
- Opting for higher dose dex and bortezomib for 1 cycle to rapidly decrease light chain burden
- Transition to VRd



Cyclophos 250 mg/m2 BID

Dex 40 mg

Bortezomib 1.3 mg/m2 subq

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55 year old NDMM with AKI

- PLEX x 3
- Received one cycle of intensified CyBorD
  - KLC declined to 1147 after first week
  - KLC 165 after cycle 1
  - Creatinine improved to 1.5 after cycle 1
- Planned transition to VRd -> Stem cell transplant
- Pre-transplant creatinine 1.0

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Practice Points

- AKI in newly diagnosed MM is frequently multifactorial
- Understanding the pathophysiology may help with assigning treatment
- 24 hour urine and serum free light chain findings can help identify cast nephropathy
  - Monoclonal light chains in 24 hour urine with minimal albuminuria + high involved serum free light chains argue for the diagnosis of CN
  - Significant albuminuria argues against
- Plasma exchange may still have a role in this narrow patient population, though available studies have not directly addressed the question in a way directly applicable to practice
- Support with hydration avoiding nephrotoxins (such as IV contrast) is key
- **Rapid cessation of light chain production is necessary for renal recovery**

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