Challenging cases in AKI-myeloma

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National Amyloidosis Centre, UCL

Case 1

- Patient DB 58 years old

- Presented with 2 weeks of severe L thigh and back pain
- Fatigue

- o/e BP 130/70, mild oedema, chest clear, JVP↑

- AKI
  - Urinalysis: 3+ Blood, 3+ protein
  - Creat 666, eGFR <15, Bic 20, Ca 2.36, Alb 41
  - Hb 74 WCC 5.6 Plat 169
  - Clotting NAD
  - uPCR 419 mg/mmol

DB continued

Acute renal screen

- Immunology negative
- Virology negative
- Blood film – no MAHA
- USS – normal size kidneys, no obstruction
- Free lambda band on IF only
- Urine lambda BJP
- sFLC kappa 14.5 mg/L, lambda 4740.0 mg/L, R <0.01

DB continued

Acute renal screen

- Immunology negative
- [illegible]
- [illegible]
- [illegible]
- Free lambda band on IF only
- Urine lambda BJP
- sFLC kappa 14.5 mg/L, lambda 4740.0 mg/L, R <0.01

What is the differential diagnosis?

Spectrum of Immunoglobulin related renal injury

Primary Mechanism	Secondary Mechanism	Example
Excess IgM	Hyperviscosity	Waldenstrom's macroglobulinaemia
Abnormal LC binding to THP	Blockage of distal tubule	Cast nephropathy
Binding to BM	Glomerular injury	Monoclonal Ig deposition diseases
IgM RhF binding to IgG	Immune complex formation	Cryoglobulinaemia
Aggregation	Tissue deposition	AL amyloidosis

DB - Likely diagnosis?

- Amyloidosis
- Cast nephropathy
- LCDD
- ATN

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- Amyloidosis
- Cast nephropathy
- LCDD
- ATN

WHO WOULD LIKE TO PERFORM RENAL BIOPSY?

Risk of Renal biopsy in MGRS?

The Incidence of Major Hemorrhagic Complications After Renal Biopsies in Patients with Monoclonal Gammopathies

Richard Fish,* Jennifer Pinney,† Poorva Jain,‡ Clara Addison,§ Chris Jones,* Satish Jayawardene,* John Booth,† Alexander J. Howie,‖ Tareck Ghonemy,§ Shahista Rajabali,§ David Roberts,§ Lucy White,§ Sofia Khan,§ Matthew Morgan,§¶ Paul Cockwell,§¶ and Colin A. Hutchison§¶

Clin J Am Soc Nephrol 5: 1977–1980, 2010

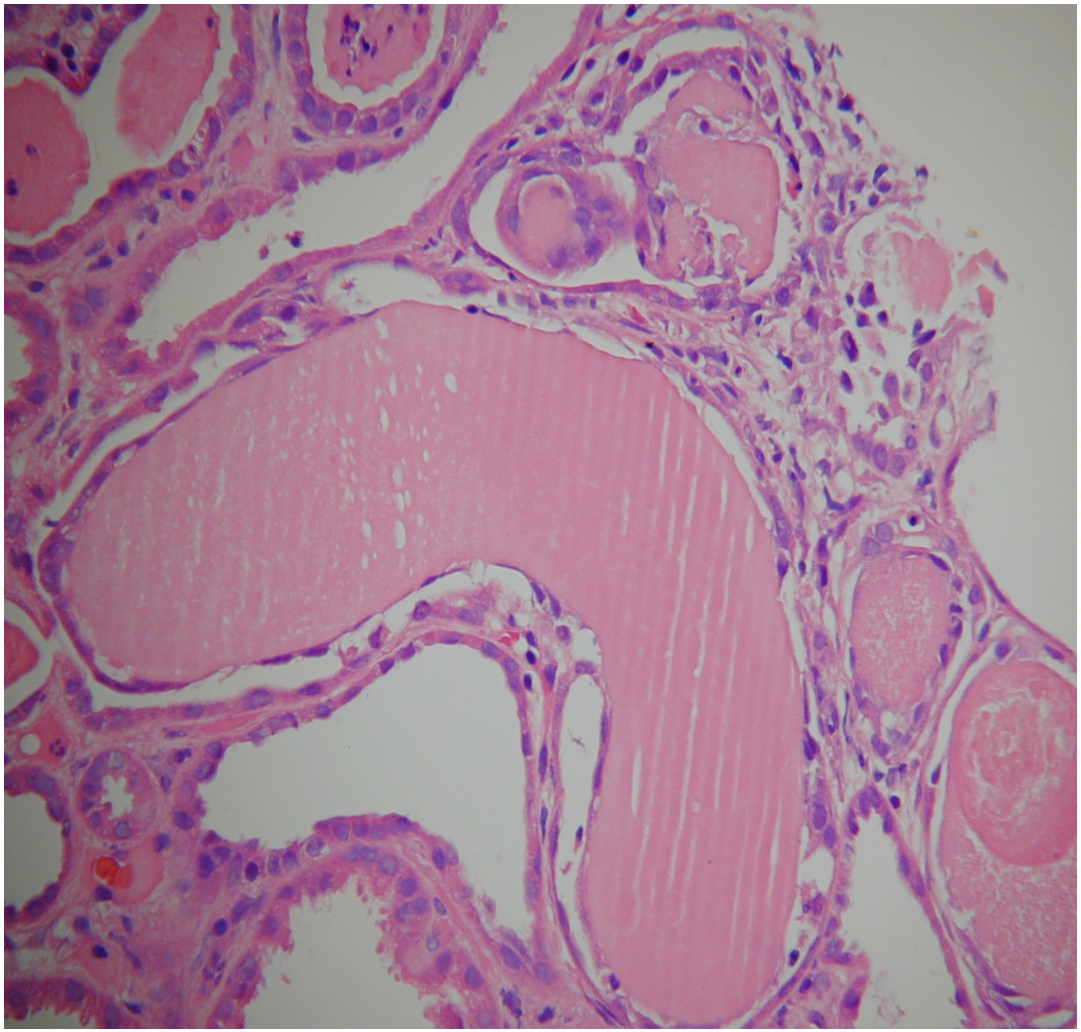
Aim: To determine the incidence of significant haemorrhagic complications after renal biopsies in patients with monoclonal gammopathies (MGRS)

Methods: Retrospective review of 1993 unselected renal biopsies from 4 UK renal units

Results: Haemorrhage in 4.1% of 148 patients with MGRS vs 3.9% of non-MGRS (P=0.88)

Conclusions: Rate of major haemorrhagic complications after percutaneous renal biopsy not significantly greater in patients with MGRS

Cast nephropathy / Myeloma kidney



Accounts for over 80% of severe renal failure in multiple myeloma

Direct consequence of high serum FLC levels

Treatment target to reduce FLCs?

DB – Further Investigations

- 60% lambda light chain restricted plasma cells on BM trephine
- Multiple lytic lesions on skeletal survey

DB – Further Investigations

- 60% lambda light chain restricted plasma cells
-

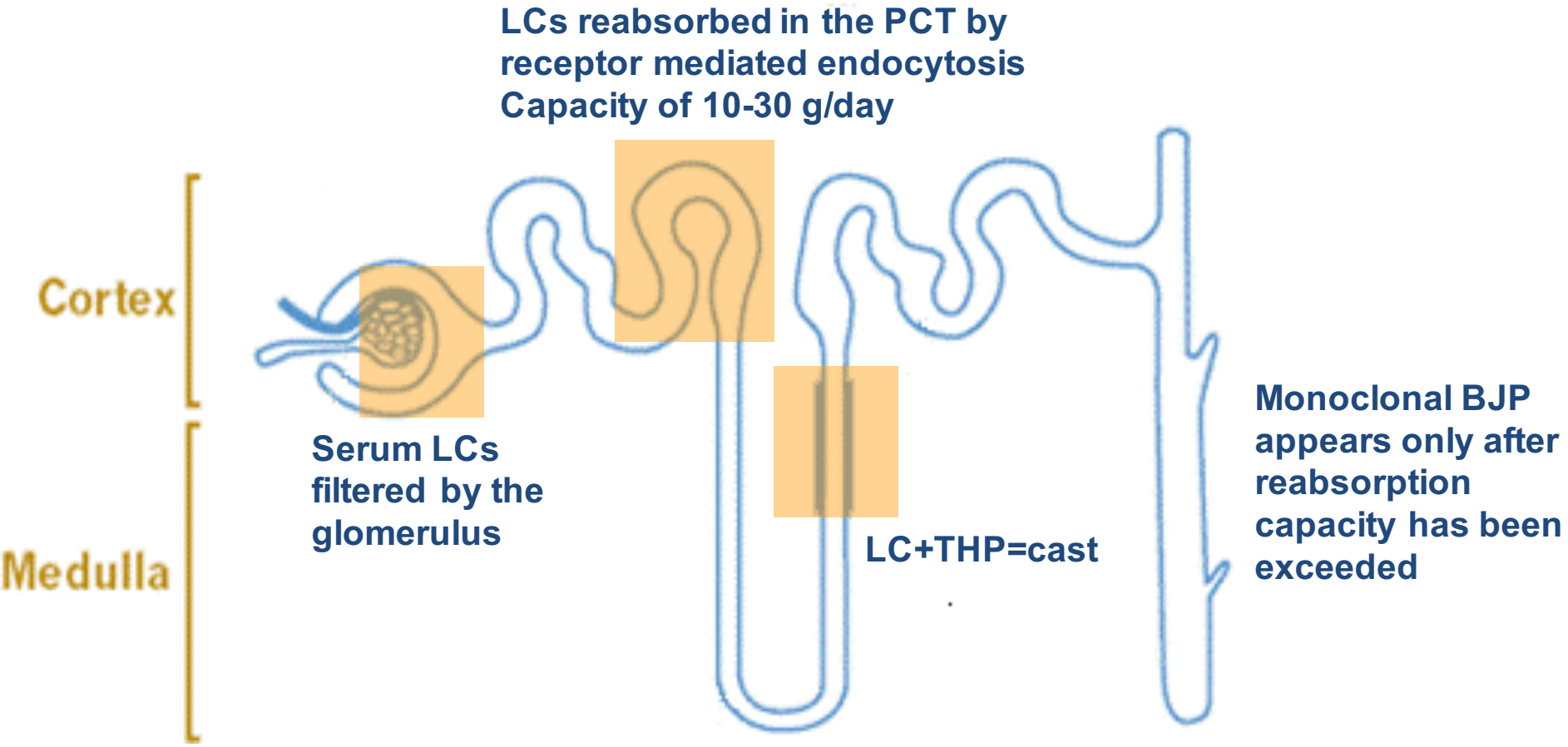
Final diagnosis

Cast nephropathy (myeloma kidney)

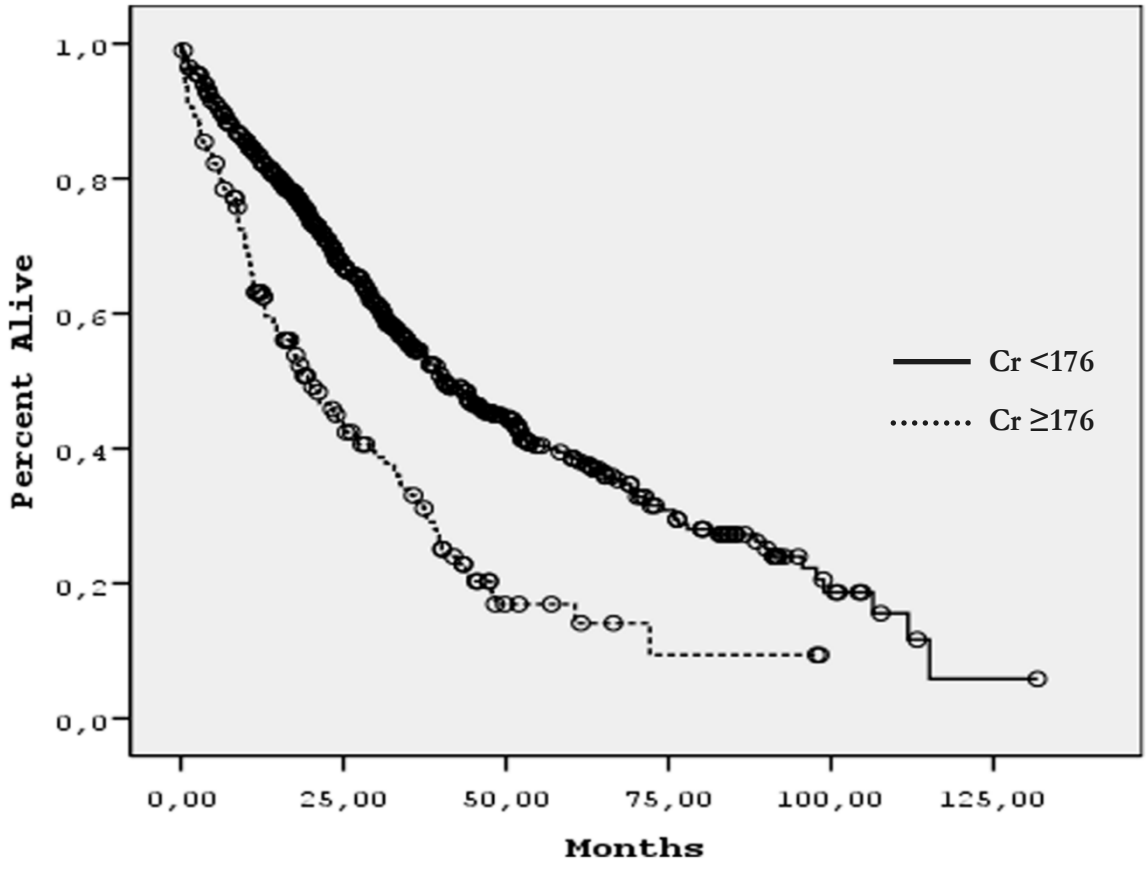
Light chain multiple myeloma

Pathogenesis of cast nephropathy

Normal production of polyclonal FLC is ~ 500 mg/day

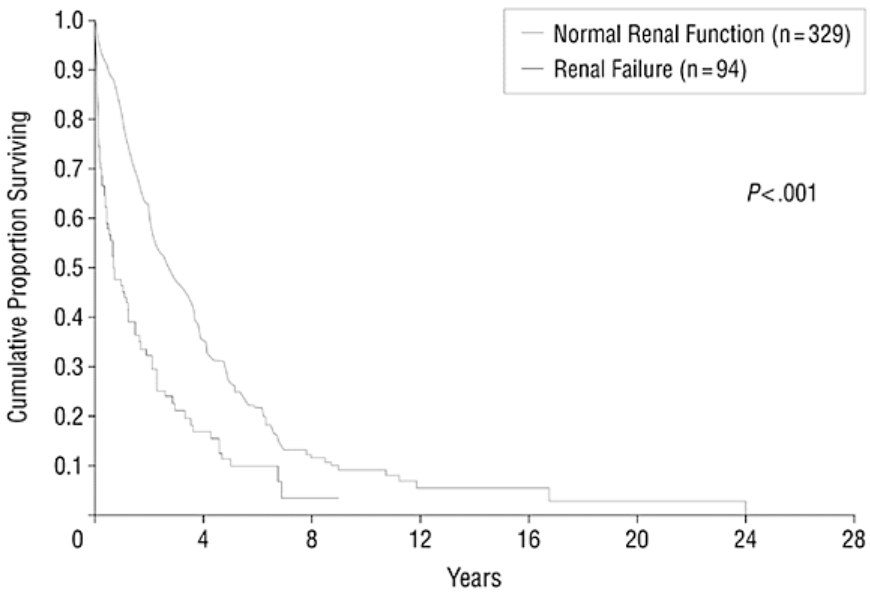


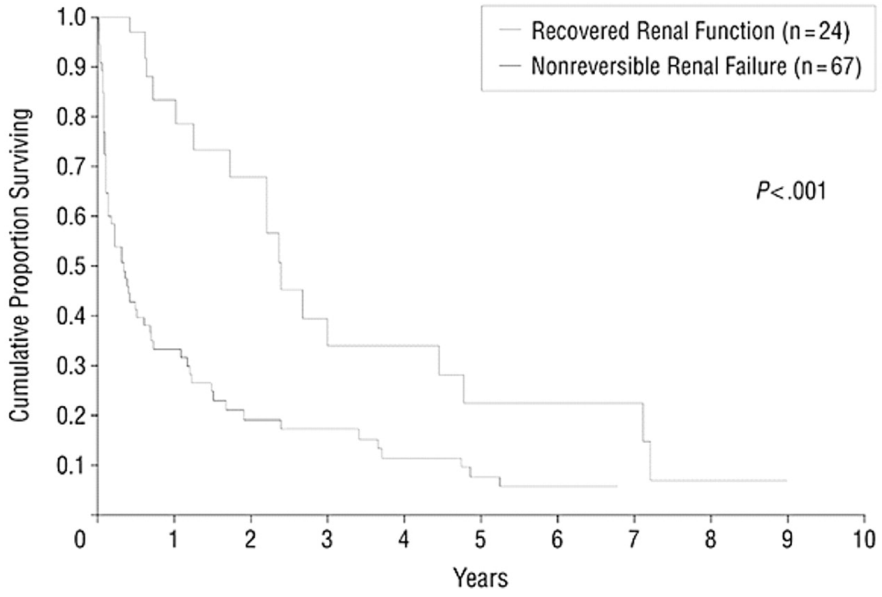
Survival in multiple myeloma according to creatinine at presentation



Eleutherakis-Papaiakovou *et al*, Leuk & Lymph 2007;48:337-341

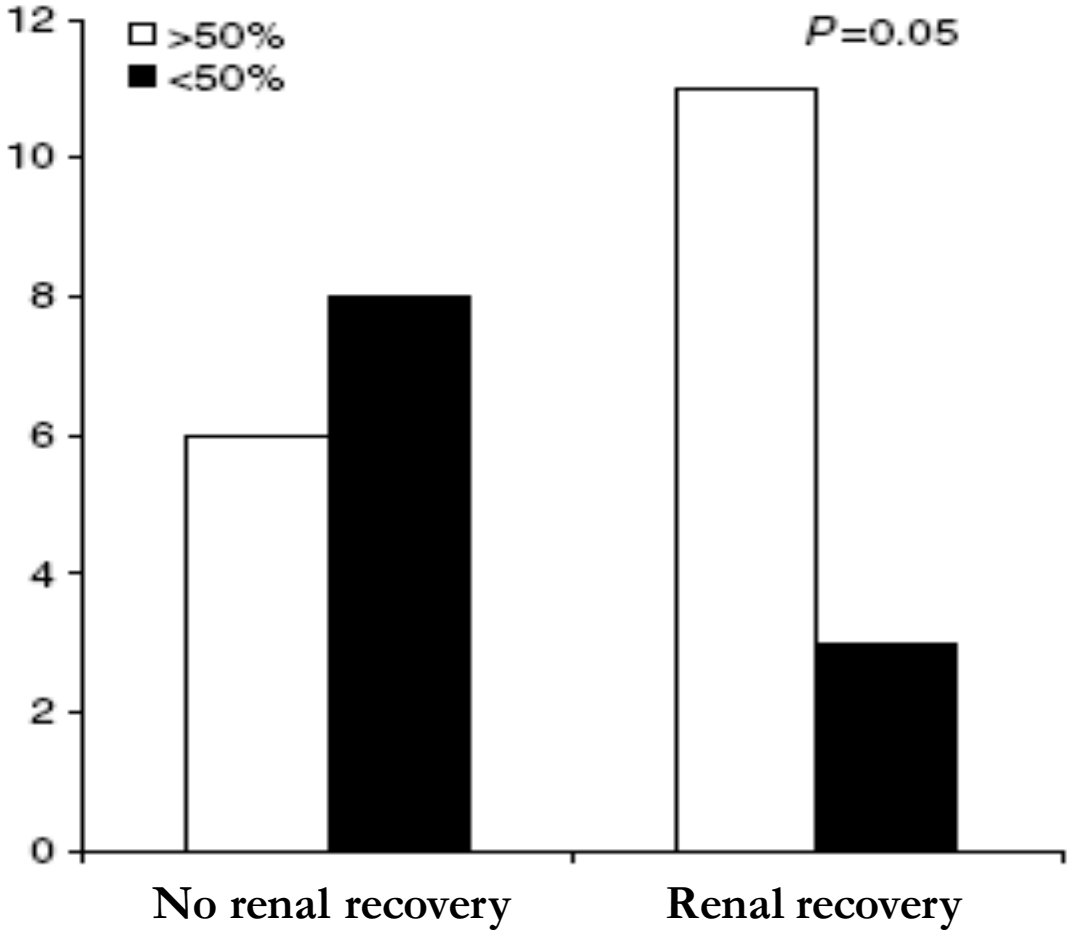
Impact of renal recovery on prognosis in MM





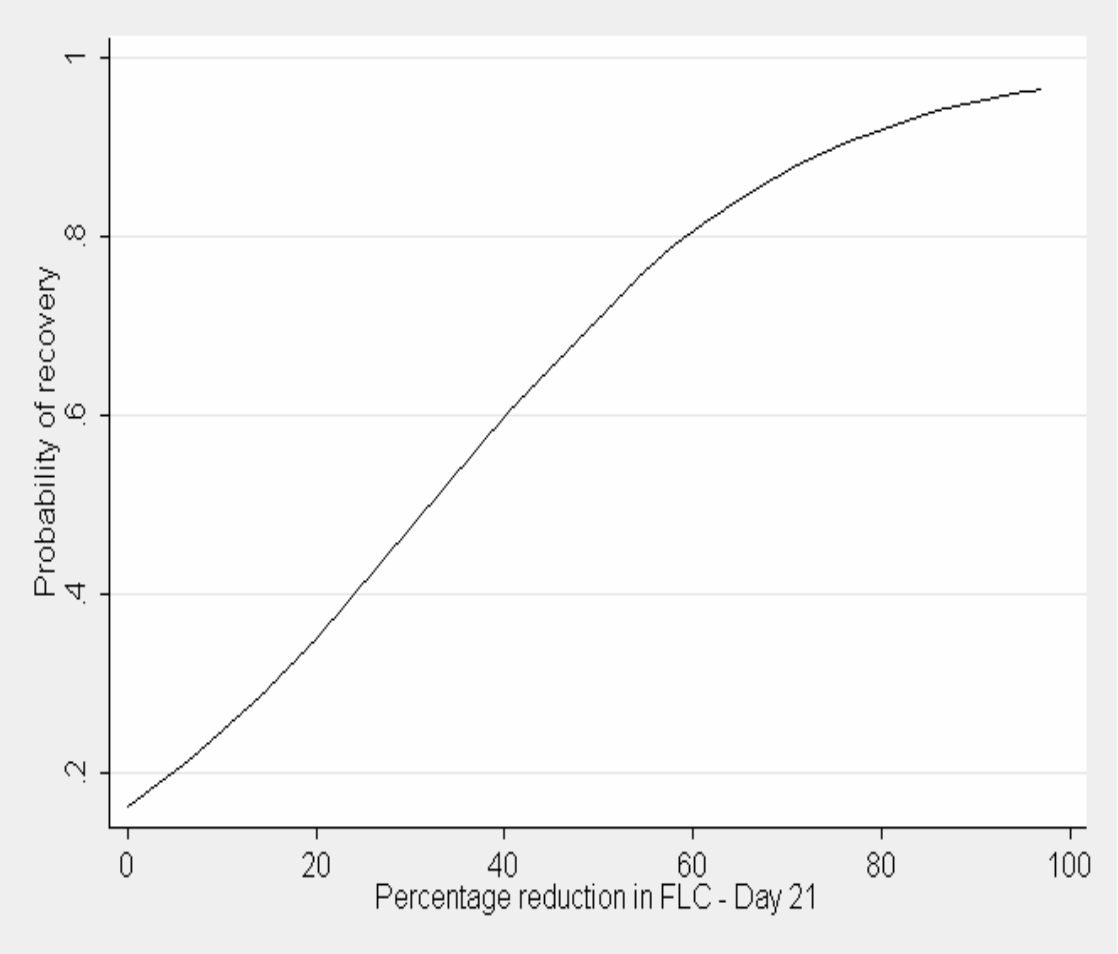
Bladé et al, Arch Intern Med 1998;158:1889-1893

Reductions in serum FLCs improves renal outcomes in myeloma kidney



Leung *et al*, Kidney International, 2008

Probability of renal recovery from cast nephropathy

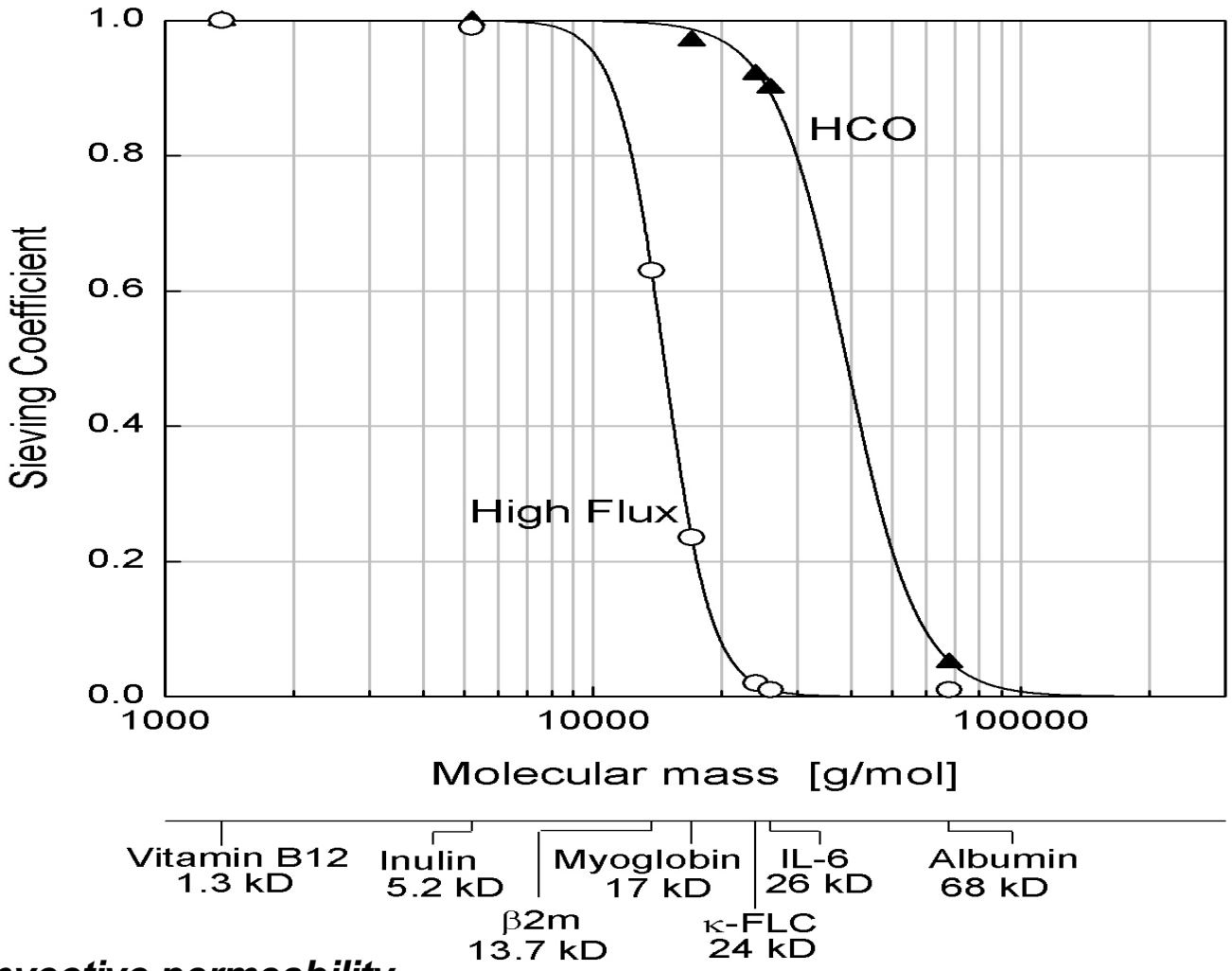


For 80% of the population to have renal recovery there must be a 60% reduction in sFLCs

39 patients with cast nephropathy: Birmingham + Mayo

HCO Membrane

Increased permeability for mid-molecules



Convective permeability

Treatment of AKI secondary to multiple myeloma with chemotherapy and extended high cut-off dialysis

Pilot study

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

Outcomes:

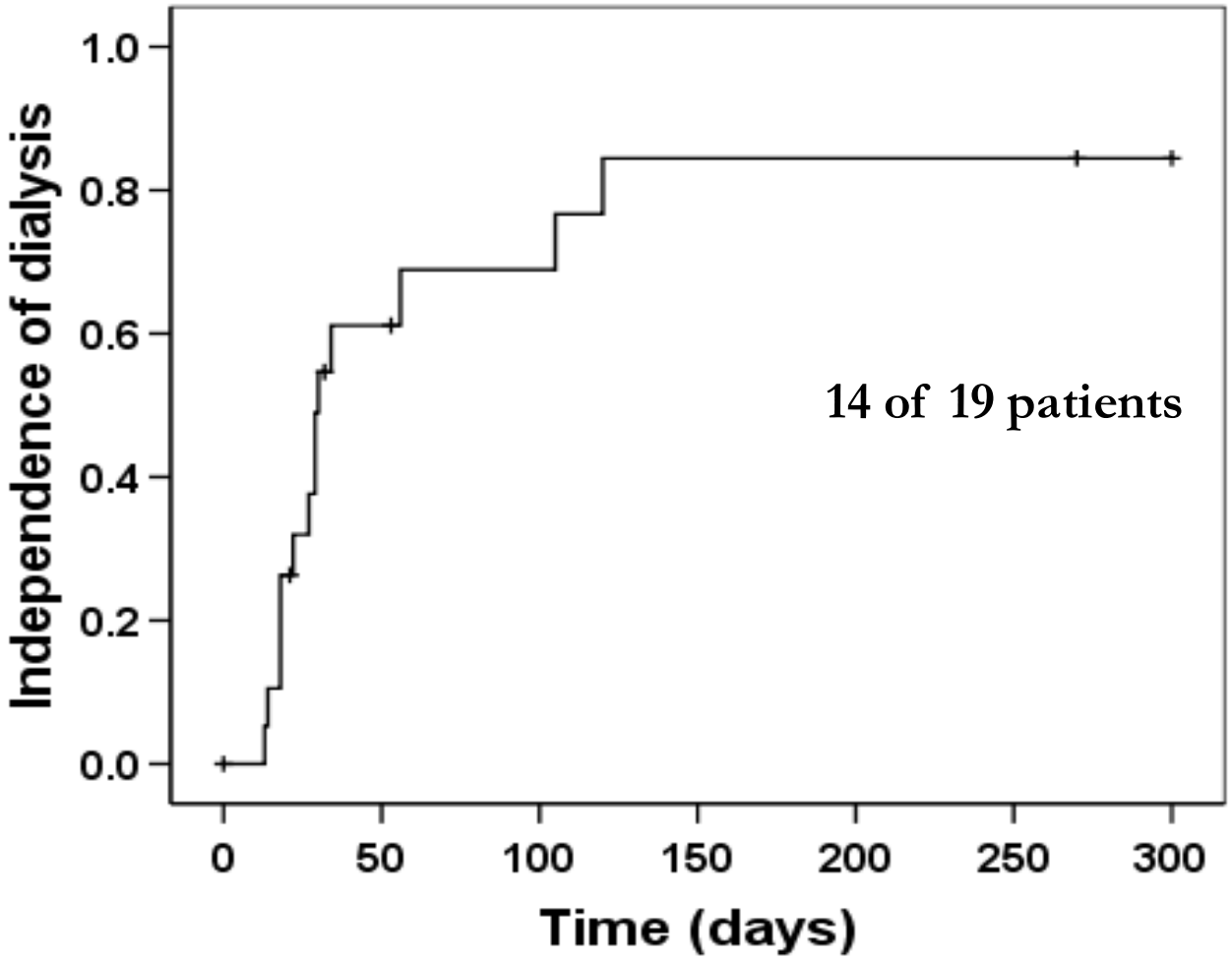
- Reduction in serum FLC concentrations
- Recovery of renal function + patient survival
- Study population compared with a case matched historical control population

Of 27 multiple myeloma patients with dialysis dependent renal failure assessed, 19 meet inclusion criteria

Clin J Am Soc Nephrol 4: 745–754, 2009. doi: 10.2215/CJN.04590908

CJASN

Recovery of renal function



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CJASN

European trial of free LIght chain removal by exTENded haemodialysis in cast nephro-pathy (EuLITE): a randomised control trial

CI: Paul Cockwell

A randomized control trial of FLC removal HD versus standard care

EuLITE
RCT

Inclusion criteria:

- *De novo* multiple myeloma (IMWG criteria BJH 2003)
- Abnormal sFLC (abberant >500 mg/L)
- New dialysis dependent renal failure (eGFR<15)
- Cast nephropathy on renal biopsy

Exclusion criteria:

- Chronic kidney disease
- Contra-indication to chemotherapy
- Amyloidosis or LCDD
- Significant cardiac disease, neuropathy, or liver disease

Outcome measures

EuLITE
RCT

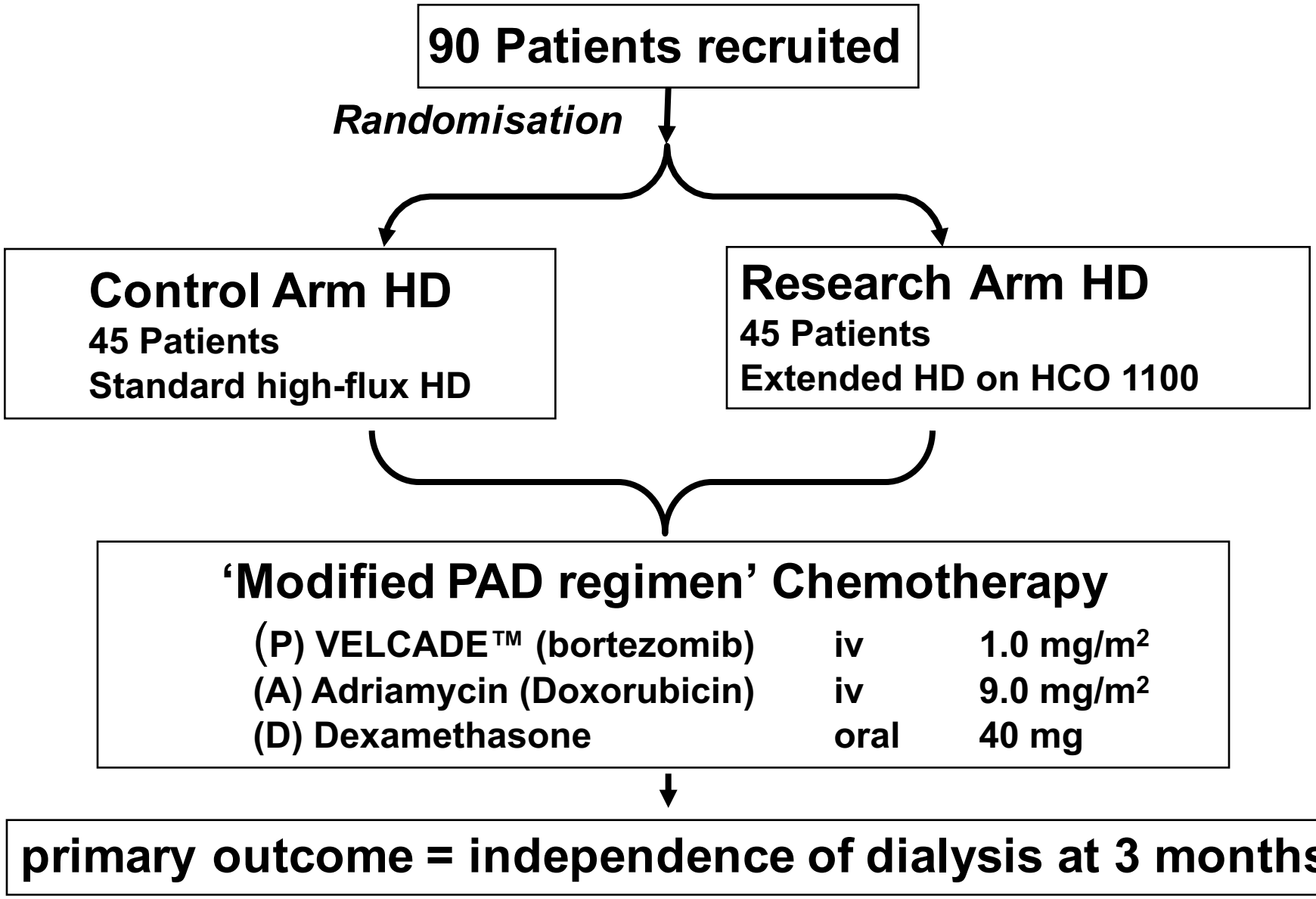
Primary outcome:

- Independence of haemodialysis at 3 months from presentation

Secondary outcomes:

- Reductions in serum FLC concentrations
- Time on haemodialysis
- Survival and haematology outcomes

Randomised and controlled



Patient DB – Clinical course

Enrolled into EuLITE

- Standard dialysis arm
- 8 cycles PAD chemotherapy
- Clonal CR
- Dialysis independent at 6 months (did not achieve primary outcome) – Creat ~200 µmol/L

Patient DB – Clinical course

Enrolled into EuLITE

- Standard dialysis arm
- 8
- C
- Dialysis independent at 6 months (did not achieve primary outcome) – Creat ~200 µmol/L

Who would consolidate with a melphalan stem cell transplant?

DB continued

- January 2013
  - Clonal relapse (12 months after Dx)
  - Dexamethasone, then Stem cell transplant (melphalan 140 mg/m^2), March 2013
  - Day 100 BM biopsy – 5% plasma cells
  - Creatinine 182
- August 2013
  - Pain from # lumbar vertebra
  - Lenalidomide/dexamethasone & kyphoplasty
- June 2014
  - Progressive spinal disease
  - Velcade / Thalidomide / Dexamethasone (VTD)
  - **Daughter's wedding**
- September 2014
  - Creatinine 148, eGFR 32 ml/min, being considered for SCT #2

DB continued

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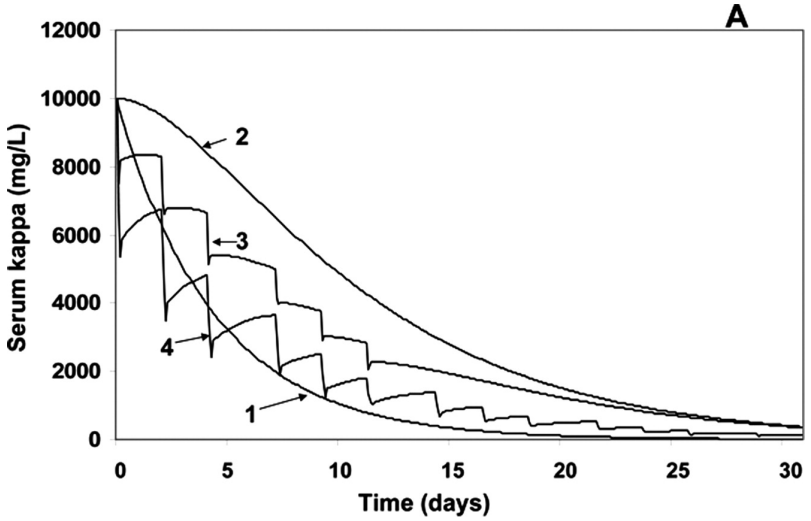
  - Clonal relapse (12 months after Dx)
  - Dexamethasone, then Stem cell transplant (melphalan 140 mg/m^2), March 2013
  -
  -
- Aug
  -
  -
- Jun
  -
  -
  - **Daughter's wedding**
- September 2014
  - Creatinine 148, eGFR 32 ml/min, being considered for SCT #2

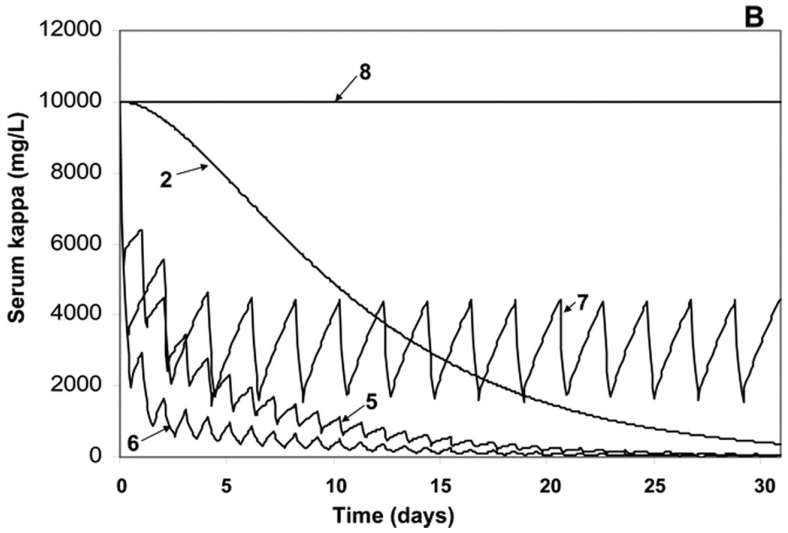
EuLITE

High proportion of patients from both arms became dialysis independent

Full trial results awaited

Simulations of LC removal with high cut-off dialysis membrane





1. 100% tumour kill, RE removal only
2. 10% tumour kill/day, RE removal only
3. 10% tumour kill/day, 3.5L PEX x 6
4. 10% tumour kill/day, HD 4h x 3 wk
5. 10% tumour kill/day, HD 4h/day
6. 10% tumour kill/day, HD 12h/day
7. No tumour kill, HD 8h x 3 wk

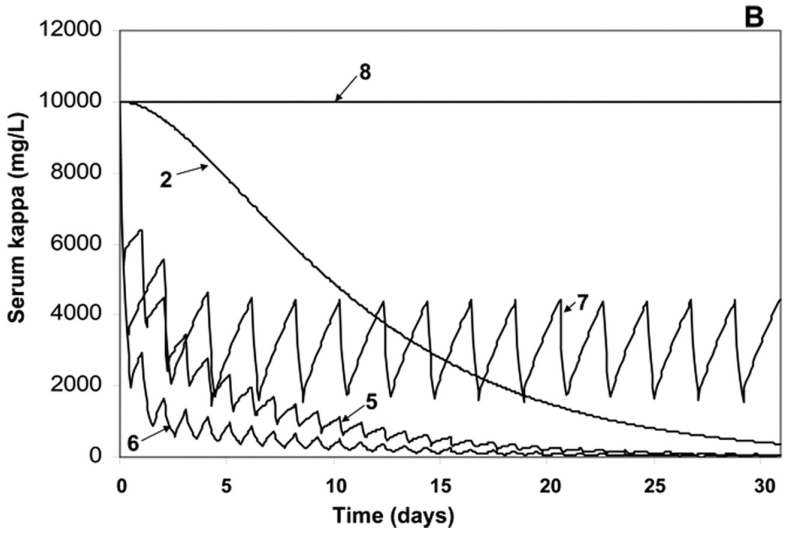
Hutchison et al. J Am Soc Nephrol 2007;18:886-895

Simulations of LC removal with high cut-off dialysis membrane

1. 100% tumour kill, RE removal only
2. 10% tumour kill/day, RE removal only
3. 10% tumour kill/day, 3.5L PEX x 6
4. 10% tumour kill/day, HD 4h x 3 wk

Cast nephropathy is a renal-AKI emergency

Treating the clone with chemotherapy is priority



Hutchison et al. J Am Soc Nephrol 2007;18:886-895

Case 2

- Patient MK — 39 yr old male

- Abdominal pain
- Oedema and dyspnoea

- o/e — ECOG 4, BP 130/80, anasarca, bilat pleural effusions

- AKI — Urinalysis: 3+ Blood, 3+ Protein
  Cr 235, eGFR 28, alb 28
  Bili 25, ALP 1822, GGT 2258, AST 220, ALT 158
  Hb 147, WCC 17.1, Plt 548
  Clotting normal
  uPCR 390 mg/mmol

MK continued

- Acute renal screen
  - Immunology negative
  - Virology negative
  - USS: normal size kidneys
  - No paraprotein
  - Urine lambda BJP
  - sFLC: Kappa 1.4, lambda 466, R <0.01

MK continued

- Acute renal screen
  - Immunology negative
  - Vir
  - US
  - No
  - Urine lambda BJP
  - sFLC: Kappa 1.4, lambda 466, R <0.01

Who would biopsy?

What would you biopsy?

MK Continued

- Biopsy Options
  - Liver biopsy
  - Renal biopsy
  - Fat biopsy (suspicion of amyloidosis)
  - Rectal biopsy

MK Continued

- Biopsy Options
  - Liver biopsy
  - Ren
  - Fat
  - Rec

Liver biopsy performed

Amyloid

IHC: AL (lambda) type

MK continued

- Amyloid ‘Staging’ investigations
  - ECG: small complexes
  - ECHO: 14 mm LV walls, grade II DD, EF 60%
  - NT-proBNP 1200 pmol/L, TnT 0.030 ng/ml
  - SAP scan: large amyloid load; liver, spleen, kidneys
  - BM biopsy: 45% lambda restricted plasma cells
  - Skeletal survey: no lytic lesions

MK continued

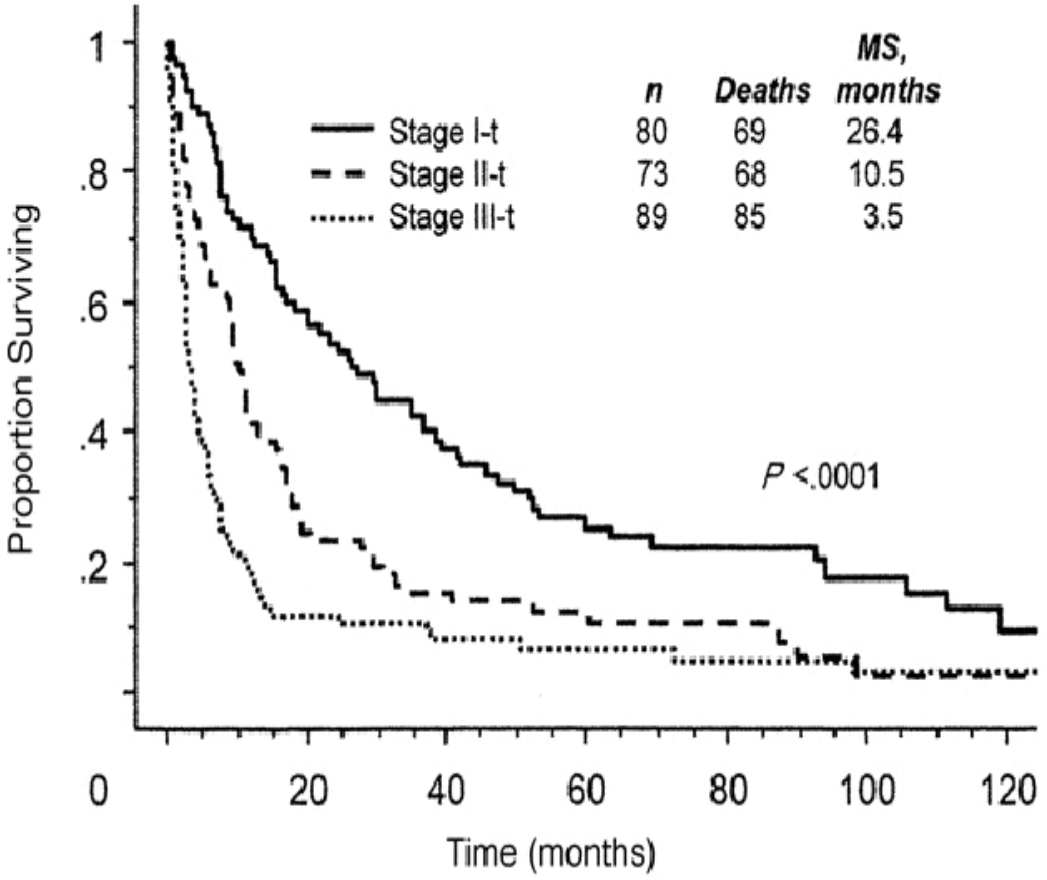
- Amyloid 'Staging' investigations

Final diagnosis

Systemic AL amyloidosis
Renal, hepatic, cardiac, (splenic) involvement
Mayo stage II disease

Lambda light chain myeloma

‘Mayo’ Staging of AL amyloidosis



Dispenzieri A *et al*, J Clin Oncol 2004;22:3751-7

Patient MK - Clinical course

Date	Booking	Cr	eGFR	CrCl	Alb	UPT 24hr	Bili	ALP	GGT	ALT	BNP	TnT	CRP	SAA	IgA	IgG	IgM	Kappa 3.3-19.4 (mg/l)	Lambda 5.7-26.3 (mg/l)	FLC Ratio 0.26-1.65	dFLC Resp	PP Outcome	PP g/L	BJP Class	BJP Quantity	Drugs
2012-03-18	0																	1.4	466.0	0.00 *	0					
2012-06-07	53538	235	28	40	28	10.4	25	1822	2258	158	1200	.303	24	22.3	1.8	1.9	1.1	12.4	61.3	0.20	89	None	0	Lambda		CVD
2012-06-29	0																	14.2	20.3	0.70	99					
2012-08-16	0																	14.6	9.8	1.49	100					
2012-09-13	0																	14.8	10.8	1.37	100					
2012-09-20	54873	151	46	64	23	5.4	13	1417	2406	74	29		3		0.8	0.9	0.9	14.7	16.0	0.92	100	None		None		
2012-11-09	0																	20.6	19.2	1.07	100					
2012-11-30	0																	19.9	15.6	1.28	100					
2013-01-14	0																	15.5	12.9	1.20	100					
2013-01-29	56524	257	25	35	30	5.9	3	495	1108	46	18		1		0.7	1.0	0.8	15.9	10.7	1.49	100	None		None		
2013-02-11	0																	19.1	12.3	1.55	100					
2013-03-20	0																	16.9	15.1	1.12	100					
2013-05-22	0																	12.1	9.5	1.27	100					VelDex
2013-07-15	0																	16.8	16.5	1.02	100					
2013-07-30	59190	183	37	58	27	9.4	<2	340	566	30	9		1		0.5	1.0	0.7	9.8	21.4	0.46	98	None		None		
2013-09-06	0																	12.9	14.8	0.87	100					
2013-11-27	0																	15.3	22.1	0.69	99					
2014-05-06	63896	246	26	38	34	6.7	3	330	674	56	26		1		1.6	3.3	0.5	26.8	26.5	1.01	100	None		None		Mel140
2014-06-10	0																	20.9	22.1	0.95	100					
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2014-05-06	63896	246	26	38	34	6.7	3	330	674	56	26		1		1.6	3.3	0.5	26.8	26.5	1.01	100	None		None		Mel140
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2013-05-22	0																	12.1	9.5	1.27	100					VelDex
2013-07-15	0																	16.8	16.5	1.02	100					
2013-07-30	59190	183	37	58	27	9.4	<2	340	566	30	9		1		0.5	1.0	0.7	9.8	21.4	0.46	98	None		None		
2013-09-06	0																	12.9	14.8	0.87	100					
2013-11-27	0																	15.3	22.1	0.69	99					
2014-05-06	63896	246	26	38	34	6.7	3	330	674	56	26		1		1.6	3.3	0.5	26.8	26.5	1.01	100	None		None		Mel140
2014-06-10	0																	20.9	22.1	0.95	100					
2014-07-08	0																	18.5	18.4	1.01	100					
2014-08-12	0																	18.1	19.3	0.94	100					
2014-09-08	0																	23.5	18.9	1.24	100					
2014-10-10	0																	23.8	21.7	1.10	100					

MK continued

- Returned to work in July (ECOG 4 at presentation)!
- BM biopsy day +100 after SCT – stringent CR (no detectable clonal disease)
- Ongoing improvement in proteinuria, LFTs, and NT-proBNP expected
- Stable CKD??

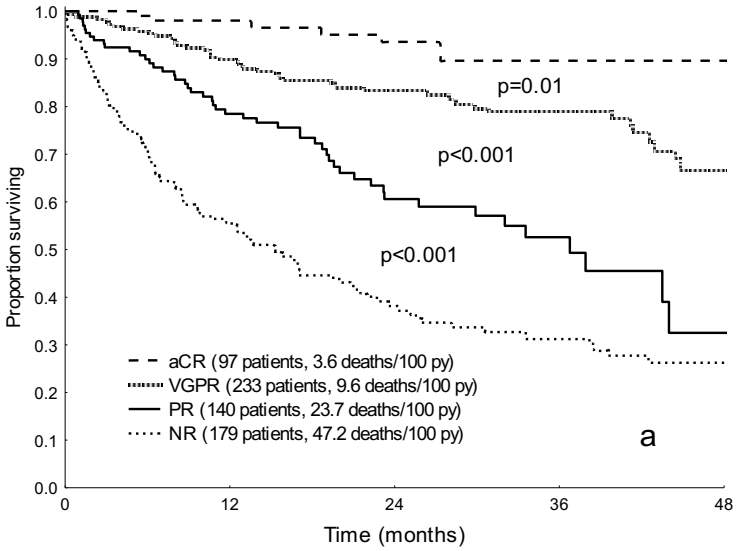
Outcomes in AL amyloidosis in relation to FLC response to chemotherapy

Renal outcome

	Renal Progression			Renal Response		
	HR	95% CI	P value	HR	95% CI	P value
FLC response						
0-49%	1			1		
50-90%	0.76	0.56, 1.04		1.64	0.99, 2.71	
>90%	0.32	0.19, 0.52	<0.0001	3.95	2.26, 6.63	<0.0001

Pinney JH *et al*, JCO 2011;29:674-81

Patient survival



Palladini G *et al*, JCO 2012;30:4541-4549

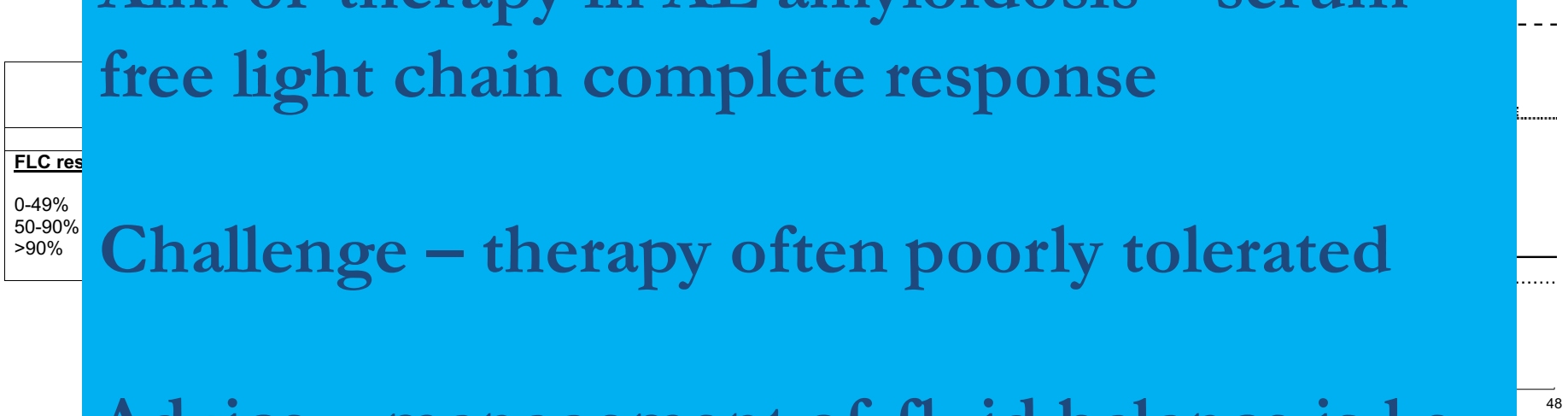
Outcomes in AL amyloidosis in relation to FLC response to chemotherapy

Renal outcome **Patient survival**

Aim of therapy in AL amyloidosis – serum free light chain complete response

Challenge – therapy often poorly tolerated

Advice – management of fluid balance is key



Pinney JH *et al*, JCO 2011;29:674-81

Palladini G *et al*, JCO 2012;30:4541-4549

Case 3

- Patient SS 42 yr old male
- Abdominal pain and vomiting
- PMH Ty II DM, HTN
- o/e Mild oedema, BP 158/101, no diabetic retinopathy
- AKI
  - Urinalysis: 3+ Protein, 2+ Blood
  - Creat 262, eGFR 24, alb 40
  - Hb 111, WCC 9.5, Plt 331
  - Clotting screen normal
  - uPCR 350 mg/mmol, kappa BJP
  - sFLC: kappa 25700 mg/L, lambda 9.8 mg/L, R 2625
  - Remaining acute renal screen unremarkable

Further Investigations

- BM biopsy – 60% kappa restricted plasma cells

- Renal biopsy – nodular glomerulosclerosis

  acute tubular injury

  staining of GBM & TBM with kappa light chain

  EM – linear electron dense deposits in GBM & TBM

Further Investigations

- BM biopsy – 60% kappa restricted plasma cells

What is the diagnosis?

- Renal biopsy – nodular glomerulosclerosis

  acute tubular injury

  staining of GBM & TBM with kappa light chain

  EM – linear electron dense deposits in GBM & TBM

Further Investigations

- BM biopsy – 60% kappa restricted plasma cells

What is the diagnosis?

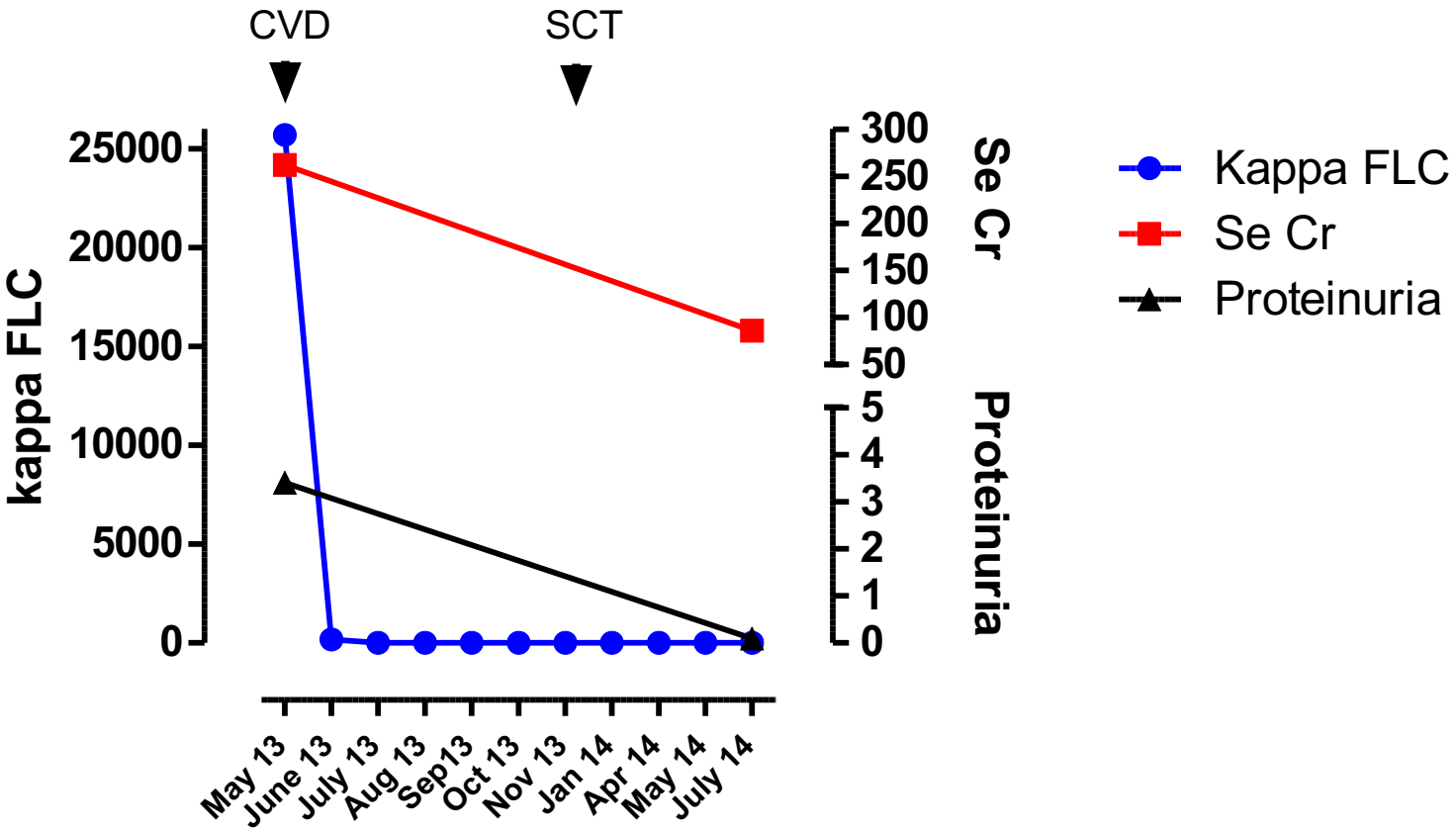
- Renal biopsy – nodular glomerulosclerosis
  acute tubular injury

Light chain deposition disease (LCDD)

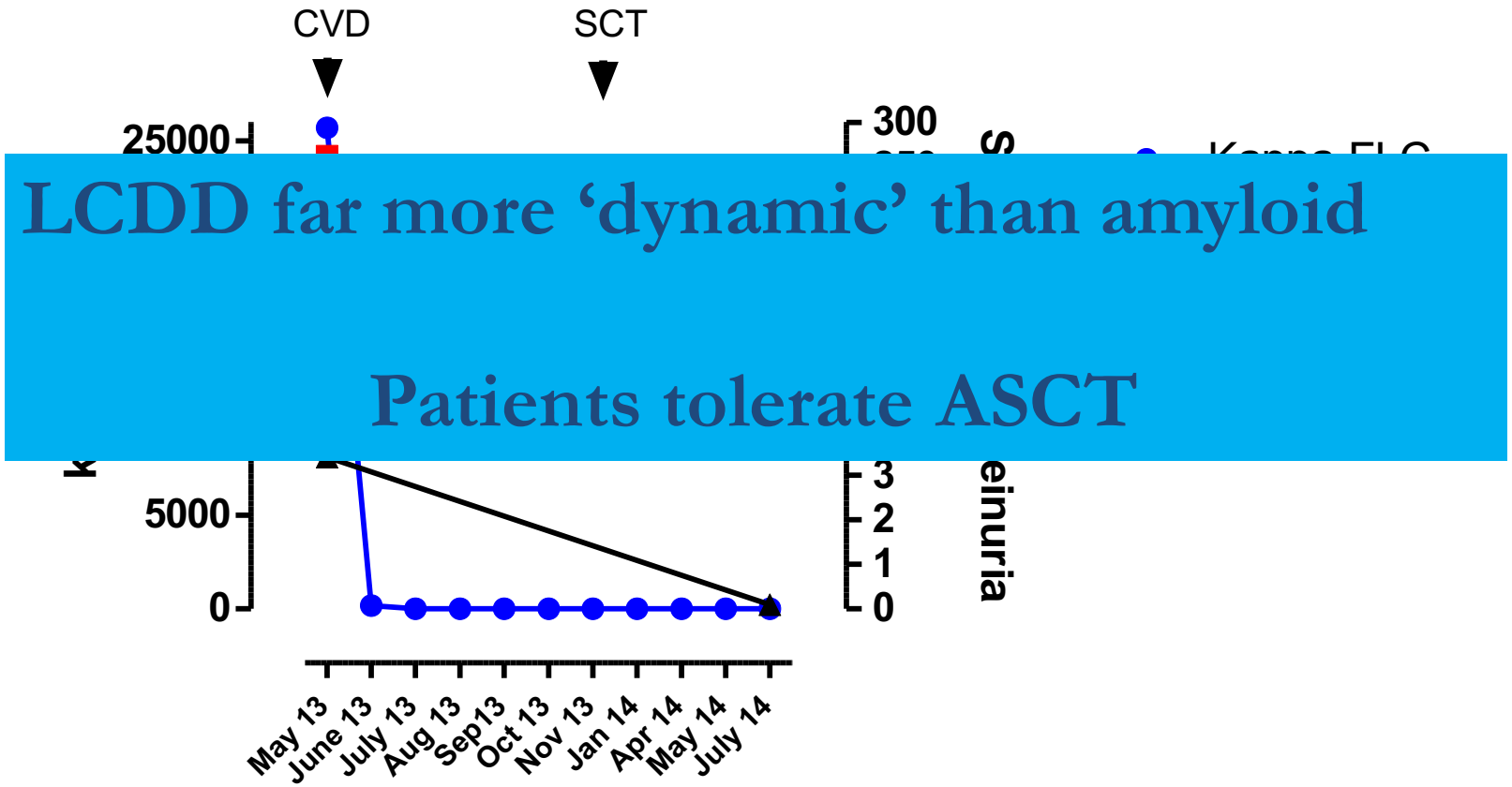
Kappa light chain myeloma

EM – linear electron dense deposits in GBM & TBM

Patient SS continued



Patient SS continued



LCDD far more 'dynamic' than amyloid

Patients tolerate ASCT

Summary & Practice Points

- Serum free light chain should be included in acute renal screen
- Renal biopsy in MGRS is worthwhile and safe
- Suspected cast nephropathy is a renal emergency and should be treated with Velcade
  - sFLC >500 mg/L, AKI