Changes in serum free light chain rather than intact monoclonal immunoglobulin levels predict outcome with therapy in patients with light chain amyloidosis

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Background

- Primary or light chain amyloidosis (AL) is characterized by deposition of immunoglobulin light chain derived amyloid fibrils
- The κ or λ light chain is secreted by clonal plasma cells
- Therapy of AL is aimed at elimination of the clonal plasma cells to reduce the serum levels of free light chain

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Background

- Response to treatment is assessed by hematological response (quicker) and organ response (often late)
- Hematological response of varying degree is a prerequisite for eventual organ response
- Current criteria* for hematological response is based on myeloma response criteria, and depends on the serum M spike by protein electrophoresis primarily

*Gertz et al. American Journal of Hematology 2005, 79:319-328

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Disadvantages of current system

- Majority of patients do not have a measurable M-spike on SPEP
- However, most patients have measurable levels of κ or λ monoclonal free light chain
- Moreover, it is the FREE light chain (rather than the intact immunoglobulin) that is the amyloid substrate and should therefore be more pertinent for organ response

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Objectives

- Examine the impact of free light chain decrease following treatment, on outcome among patients with AL
- Compare serum FLC and serum M-spike responses in terms of eventual outcome
- Identify the degree of FLC reduction associated with the best outcome

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Patients and Methods

- Two separate sets of patients were included in the current study:
  - 347 patients with AL who underwent an autologous stem cell transplant (SCT group)
  - 105 patients with AL treated with melphalan and dexamethasone combination (Mel-Dex group)
- Serum M protein and FLC measurements (FLC diff: involved-uninvolved FLC) from baseline and the lowest measurements during follow up were collected

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Methods

- The impact of the change in FLC-diff and M-spike on overall survival was examined using Cox-proportional hazards; both as continuous variables as well as by dichotomizing with specific cut-offs

- Logistic regression was used to identify cutoffs for these measurements that best predicted survival

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Baseline features: SCT group

Variable	N = 347
Age at SCT	58 years (31-75)
Gender: male (%)	199 (57%)
Number of organs involved	2 (1-3)
Duration: Diagnosis to transplant	4 mos (0.5-75)
Serum creatinine	1.1 mg/dL (0.6-12)
Serum albumin	2.7 g/dL (0.8-4.4)
Bone marrow plasma cell %	7 (0-78) %
Conditioning regimen: Reduced dose Melphalan	123 (35%)

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Baseline features: SCT group

Variable	
Serum M-Spike (gm/dL)	0.1 (0-3.9)
Serum M-spike > 1.0 gm/dL	63 (18%)
Serum M-spike > 0.5 gm/dL	106 (31%)
Serum FLC difference (Involved-uninvolved) (mg/dL)	14 (0-900)
Serum FLC-diff > 10 mg/dL	167 (57%)
Serum FLC-diff > 7.5 mg/dL	193 (66%)
Heavy chain present	52%
Kappa light chain/Lambda light chain	23% / 76%

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Results

- **First**, we examined the FLC-diff and M-Spike response (lowest/baseline) as a continuous variable for its impact on post SCT OS

	Univariate analysis			Multivariate analysis		
Variable	**n**	**HR**	**P**	**n**	**HR**	**P**
	FLC-diff > 10 mg/dL or/and M-Spike > 1.0 gm/dL					
FLC-diff	130	1.05	<0.0001	24	1.03	0.044
M-spike	52	1.03	0.02		1.002	0.9
	FLC-diff > 7.5 mg/dLor/and M-Spike > 0.5 gm/dL					
FLC-diff	152	1.05	<0.0001	37	1.04	0.0002
M-spike	78	1.01	0.02		1.007	0.6

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Results

- Next, we examined the FLC-diff and M-Spike response (50% reduction) for its impact on post SCT OS

	Univariate analysis			Multivariate analysis		
Variable	**n**	**HR**	**P**	**n**	**HR**	**P**
	FLC-diff > 10 mg/dL or/and M-Spike > 1.0 gm/dL					
FLC-diff	130	20.2	<0.0001	24	36	0.0003
M-spike	52	2.2	0.1		1.7	0.5
	FLC-diff > 7.5 mg/dLor/and M-Spike > 0.5 gm/dL					
FLC-diff	152	8.4	<0.0001	37	28	<0.0001
M-spike	78	1.8	0.1		1.1	0.9

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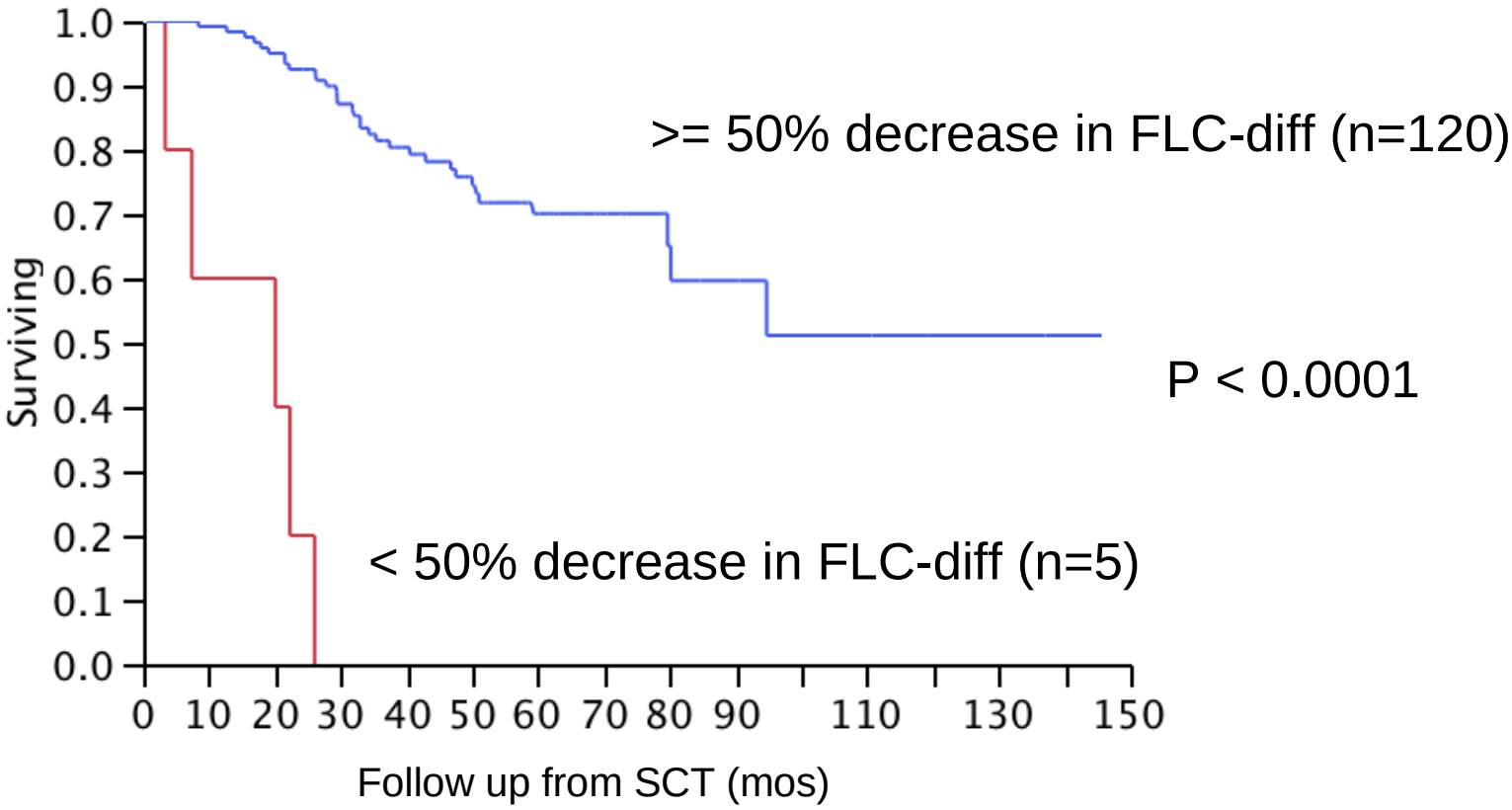
Post-SCT OS: effect of FLC-diff change



Excludes day 100 deaths

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Results: Ideal response

- Logistic regression done to identify best reduction of FLC-diff that predicts being alive at 3 years and 5 years
- The best cutoff was a 90% reduction in FLC-diff following SCT (patients with baseline FLC-diff >= 10 mg/dL)
- Results were similar when including patients with baseline FLC-diff >=7.5 mg/dL

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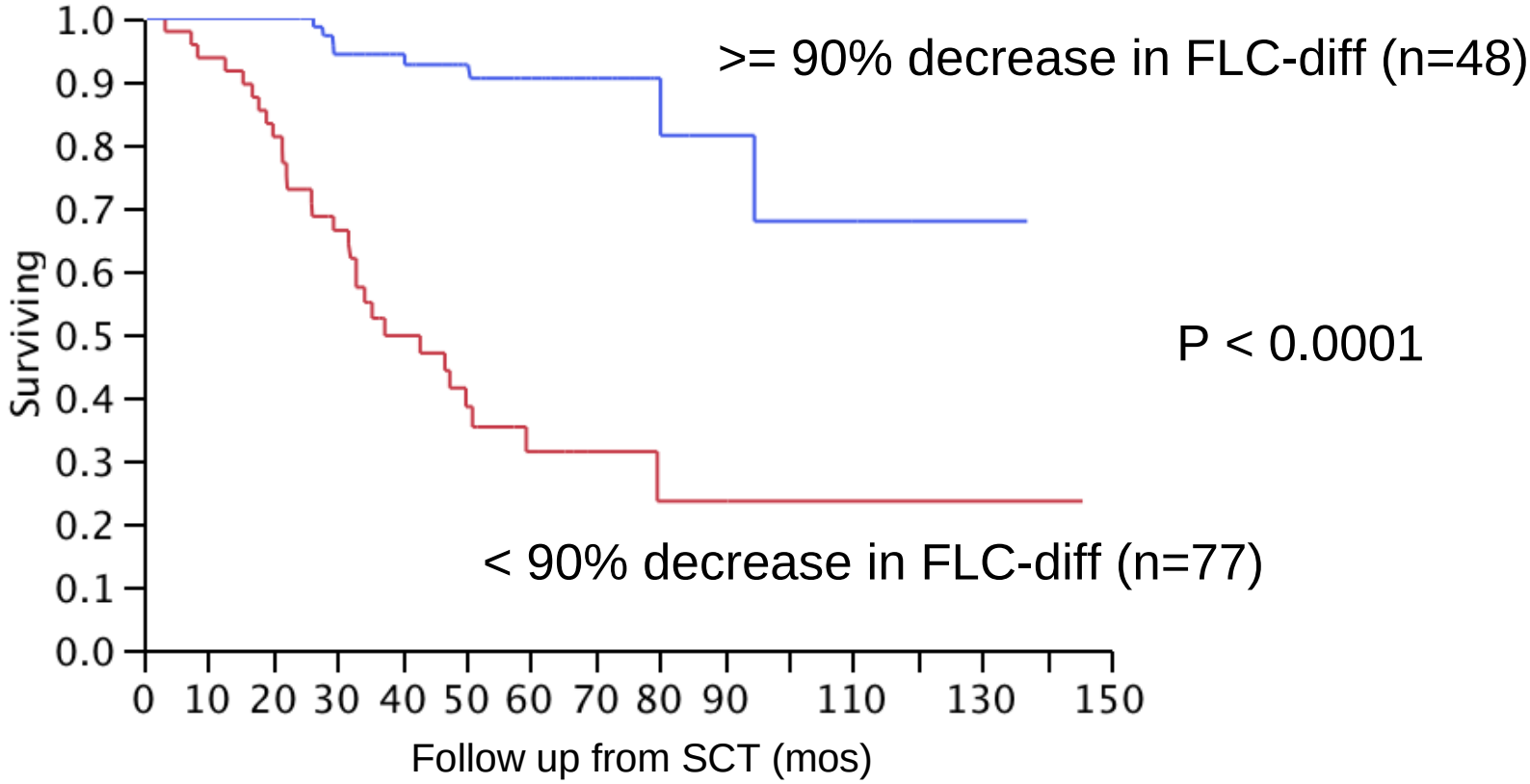
Post SCT OS: effect of FLC-diff change



Excludes day 100 deaths

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Baseline features: Mel-Dex group

Variable	(N = 105)
Age	64 (38-82) years
Gender: male (%)	71 (68%)
Number of organs involved	2 (1-3)
Duration: Diagnosis to treatment	1.2 mos (0.1-50)
Serum creatinine	1.2 mg/dL (0.5-9.4)
Serum albumin	3.6 gm/dL (1.6-4.2)
Bone marrow plasma cell %	10% (0-90)

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Baseline features: Mel-Dex group

Variable	
Serum M-Spike	0.0 (0-4.4) (gm/dL)
Serum M-spike > 0.5 gm/dL	N=22 (21%)
Serum M-spike > 1.0 gm/dL	N=13 (12%)
Serum FLC difference (Involved-uninvolved)	14 (0-900) (mg/dL)
Serum FLC diff > 7.5 mg/dL	N=84 (80%)
Serum FLC diff > 10 mg/dL	N=76 (72%)

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Results: Mel Dex group

- Results were similar to that in the SCT group with the reduction of FLC difference being a strong predictor of OS
- Number of patients with a measurable M-spike was too few for a multivariate analysis including both
- In a logistic regression model looking at 1 and 2 year survival, 83-87% reduction in FLC-diff was the best predictor

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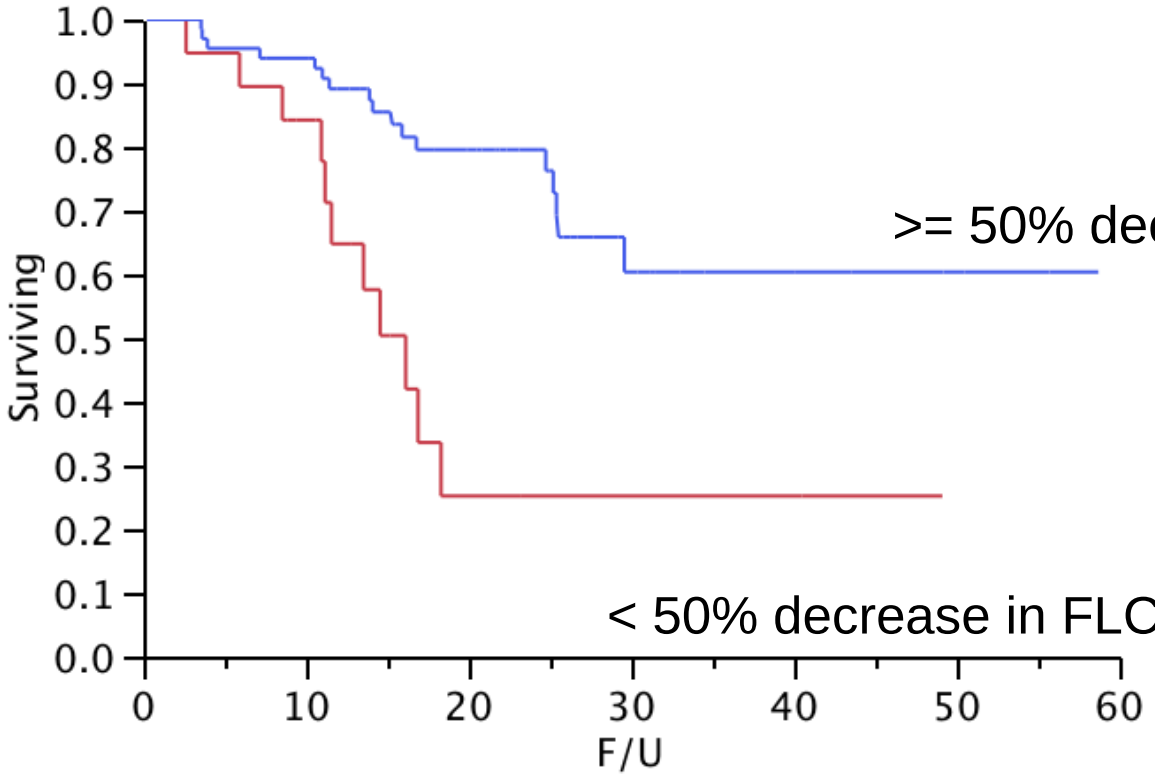
Effect of FLC reduction on OS



>= 50% decrease in FLC-diff (n=66)

P = 0.0005

< 50% decrease in FLC-diff (n=19)

Includes only patients receiving at least 3 cycles of Mel Dex

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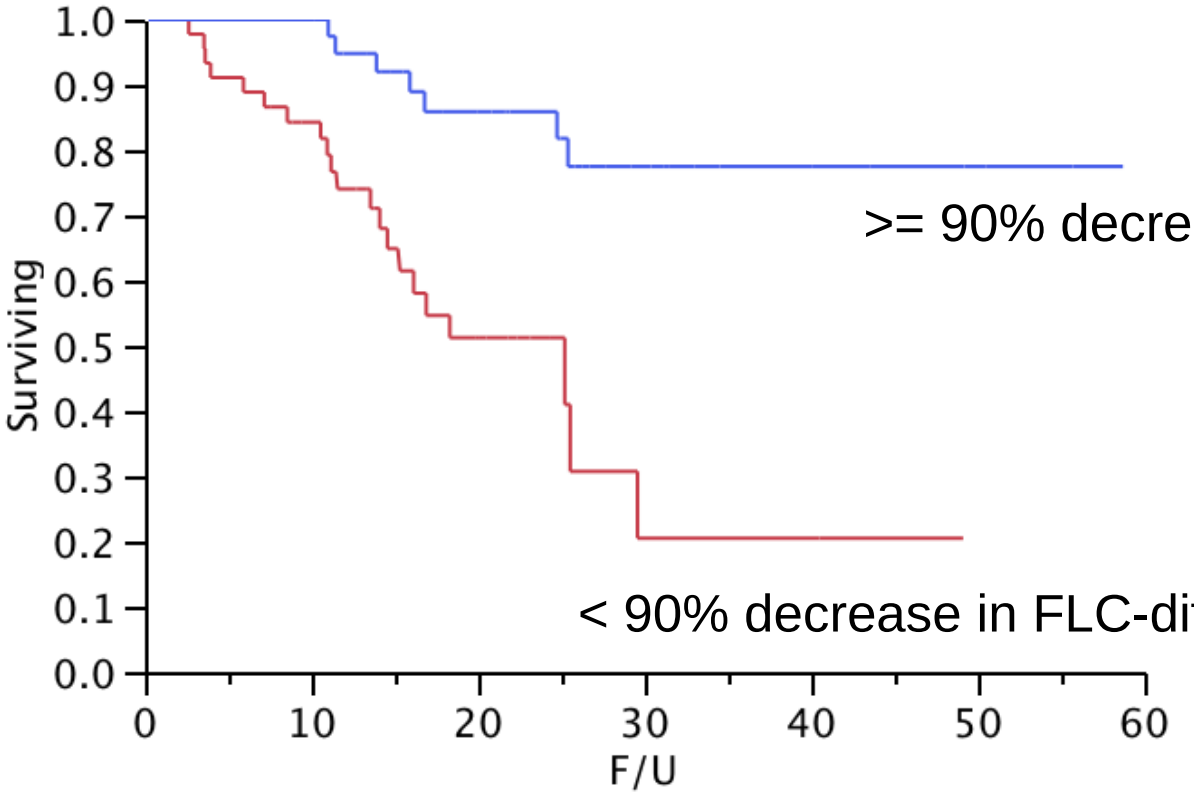
Effect of FLC reduction on OS



>= 90% decrease in FLC-diff (n=40)

P < 0.0001

< 90% decrease in FLC-diff (n=45)

Includes only patients receiving at least 3 cycles

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Conclusions

- Serum FLC difference (Involved-uninvolved FLC) should be the primary marker for following hematological response:
  - More patients are evaluable for response using FLC compared to SPEP
  - It better predicts outcome (survival) compared to M-spike by SPEP
- A 90% reduction in free light chain best predicts outcome and should be part of the response criteria akin to the VGPR in MM