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Diagnosis and monitoring for light chain only and oligosecretory myeloma using serum free light chain tests

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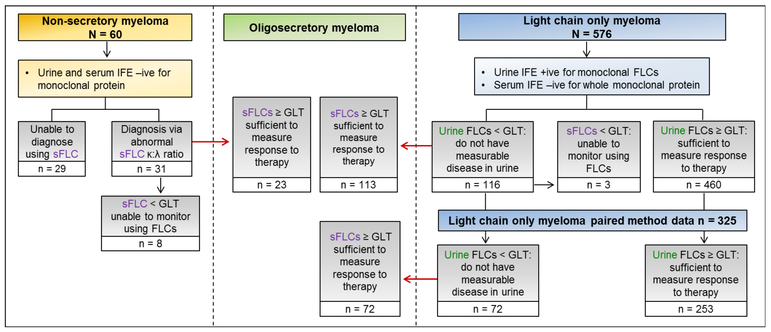
Introduction

- Free light chain (FLC) quantitation is vital for diagnosis and monitoring of light chain only (LCO) myeloma, which accounts for up to a fifth of all myeloma cases
- FLC measurement was first established in urine (uFLC) and quantitation in serum (sFLC) was not available until 2001 with the introduction of the Freelite assay
- The greater sensitivity of measuring FLC levels in serum versus urine has been shown through the detection of abnormal sFLC levels in 19/28 non-secretory (NS) myeloma patients with undetectable FLC in serum and urine by immunofixation electrophoresis (IFE) (Drayson, et al 2001)
- The sFLC test has been shown to accurately diagnose LCO myeloma and provide greater sensitivity at maximum response, where sFLC levels remained abnormal in two thirds of patients with no FLC detectable in urine (Bradwell, et al 2003)
- SFLC testing has subsequently been incorporated into IMWG guidelines for diagnosis and management of all plasma cell dyscrasias. However, these guidelines still recommend use of uFLC for measurement of response to therapy if available as more evidence is required to advocate replacement with sFLC testing
- Current guidelines are based on the Freelite assay but new sFLC methods have become available more recently, including a portable sFLC test (Seralite) that quantitates serum κ and λ FLC levels simultaneously in 10 minutes
- To enable further incorporation of sFLC measurement into clinical practice, and the utilisation of new technologies, there needs to be extensive assessment of clinical concordance between different FLC methods. It is important to evaluate how the recommended guideline thresholds for Freelite perform in clinical samples and establish appropriate thresholds for new tests, such as Seralite.
- This study aims to further verify the clinical utility of sFLC assessment and guide integration of quantitative sFLC tests into clinical practice

Methods

- Central laboratory analysis was reviewed for 5573 newly diagnosed myeloma patients enrolled in phase III national trials in the UK between 2003 and 2015. Patients classified as LCO or NS with paired serum and urine data available at disease presentation were identified
- All patient serum and urine samples were assessed by IFE. Freelite sFLC data were retrospectively evaluated on 576 patients diagnosed with LCO myeloma and 60 with NS myeloma. Where archived presentation sera were available, samples underwent further FLC analyses using the lateral flow device Seralite (n = 325) for comparison with Freelite

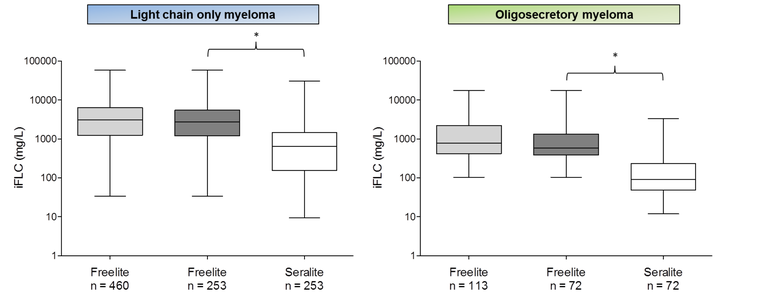


- Urine FLC guideline threshold (GLT) of ≥200 mg/g creatinine was applied
- Serum FLC GLT of ≥100 mg/L on Freelite was applied

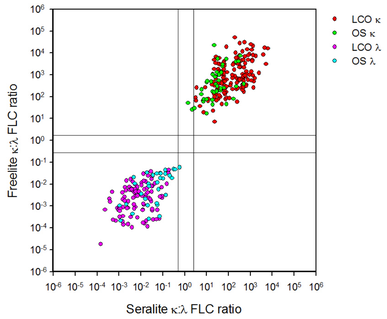
Results

1. LCO and OS myeloma at diagnosis

Independent of uFLC results, and patient grouping, the serum κ:λ ratio was abnormal on Freelite in all 576 patients thus able to sensitively diagnose patients without intact M-protein. As illustrated below, involved FLC levels on Freelite were significantly higher compared to Seralite for both LCO and OS patient groups ($p < .001$)



Despite difference in FLC quantitation between the methods, good clinical concordance was demonstrated. All LCO patients displayed an abnormal κ:λ ratio on both Freelite and Seralite (100% concordance). For OS patients, abnormal ratios were observed for all 72 patients on Freelite and 69/72 on Seralite (95% concordance). In the 3 OS patients with normal serum FLC ratios by Seralite, serum was -ive for monoclonal FLC by IFE and the Seralite monoclonals identified FLC in urine



2. NS myeloma at diagnosis

Non-secretory myeloma (N = 60)			
Elevated κ & increased ratio n = 27	Elevated λ & decreased ratio n = 4	FLC suppression (< 10 mg/L) unreliable ratio n = 18	K or λ normal or normal ratio n = 11
iFLC ≥ 100 mg/L n = 23			

By both methods, ≥ 38% of NS patients had measurable disease and could be reclassified as oligosecretory myeloma. The Seralite FLC difference (dFLC, involved minus uninvolved FLC) was able to accurately identify patients with ≥100 mg/L on Freelite, AUC = .85 (95% CI .63–.1, p <.05). A dFLC of 20 mg/L on Seralite was identified as the GLT to discriminate measurable disease at diagnosis equivalent to 100 mg/L on Freelite (92% sensitivity, 75% specificity)

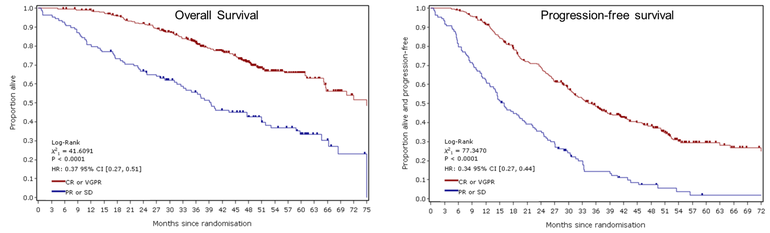
3. LCO and OS myeloma at max response

163 patients with measurable disease at diagnosis (according to both assay GLTs) had serum samples available at max response. The absolute levels of dFLC were significantly higher on Freelite compared with Seralite for both patient groups (*p <.01). However, the median percentage reduction in dFLC from presentation to max response was the same between the two methods. Further, there was little difference between the methods for response rates, with the majority of patients achieving ≥VGPR on both assays

	Light chain only n = 132		Oligosecretory n = 31	
Median	**Freelite**	**Seralite**	**Freelite**	**Seralite**
dFLC (mg/L) at presentation	3207.8*	657.5	758.8*	106.2 9
dFLC (mg/L) at max response	19.7*	7.6	3.5*	2.5
% reduction dFLC from presentation	99.3	98.7	99.7	98.3
Response Criteria				
≥ VGPR	116 (88%)	110 (83%)	26 (84%)	23 (74%)
< VGPR	16 (12%)	22 (17%)	5 (16%)	8 (26%)

4. Relationship between response by sFLC assessment and survival

Survival outcomes were explored in relation to sFLC response assigned using Freelite for all patients with measurable disease at diagnosis and follow-up data available (n = 402). Patients with ≥VGPR had significantly better OS and PFS compared to patients with VGPR. Survival was also evaluated for patients who had sFLC measured using Seralite at max response: the same relationships between response and survival outcomes were observed



5. LCO and OS myeloma at relapse

LCO (n = 34) and OS (n = 6) patients with serum samples at relapse were evaluated by Freelite and Seralite. dFLC levels measured by Freelite were higher compared with Seralite (*p < .01). Percentages increases in dFLC were also higher on Freelite, but both methods demonstrated substantial percentage increases and were able to identify a return in disease activity from remission. Relapse was identified using a FLC increase >200 mg/L on Freelite and found 100% concordance with a corresponding Seralite increase of dFLC >30 mg/L. All patients at relapse presented with an abnormal κ:λ FLC ratio; however, ≤30% of these patients had a normalised ratio at max response; thus the ratio may only be useful in identifying active disease and not remission

	All patients, n = 40	
Median	**Freelite**	**Seralite**
dFLC (mg/L) at max response	40.1*	13.7
dFLC (mg/L) at relapse	558.0*	101.2
% increase dFLC from max response	1063.3*	725.8
κ:λ FLC ratio		
% normalised ratio at max response	28%	30%
% abnormal ratio at relapse	100%	100%

Conclusions

- The sFLC κ:λ ratio was able to sensitively diagnose all LCO and OS patients independently of uFLC levels, confirming urine is not essential for the diagnosis of LCO myeloma. Serum FLC testing was able to diagnose half of NS patients, with a third of patients also suitable for monitoring using sFLCs. This confirms the benefit of sFLC testing in patients IFE negative on both serum and urine
- Response by sFLC assessment was prognostic for survival. Achieving ≥VGPR, according to either sFLC method, was associated with better overall and progression-free survival. Patients with ≥VGPR had a 66% reduced risk of death/progression and 63% reduced risk of death demonstrating the clinical utility of routine sFLC testing for sensitive patient monitoring
- At diagnosis, the recommended Freelite level of FLC >100 mg/L for measuring response was confirmed and equivalent dFLC level of >20 mg/L identified for Seralite. Relapse can be defined using a threshold of >30 mg/L increase in dFLC on Seralite, corresponding to an increase in iFLC >200 mg/L on Freelite
- In individuals sFLC levels varied between tests, with higher FLC levels observed on Freelite at all 3 time points. However, good clinical concordance was observed at diagnosis and in response to therapy
- Freelite and another FLC assay, N Latex, require nephelometric or turbidimetric analysers and often samples need to be sent away for analysis, leading to delays in receiving patient results. As a portable rapid test, Seralite could aid in the acceleration of myeloma diagnosis and facilitate prompt feedback on patient responses to anti-myeloma therapy and in monitoring for relapse

Disclosures: UoB, MD and JC own shares in Abingdon Health Ltd, who manufacture Seralite and MD advises AH Ltd