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 FL 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 IFE 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 (Seraleit) that quantitates serum and urine 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 Seraleit.
- 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 included.
- 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 Seraleit (n = 325) for comparison with Freelite.

Results

1. LCO and OS myeloma at diagnosis

Independent of sFLC test or patient group, the serum k: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 Seraleit for both LCO and OS patient groups (p < .001).

2. NS myeloma at diagnosis

Non-secretory myeloma (N = 60)

Elevated K / K or λ decrease

<table>
<thead>
<tr>
<th>Non-secretory</th>
<th>FLC</th>
<th>K or λ</th>
<th>N</th>
<th>R</th>
<th>FLC &lt; 10 mg/L</th>
<th>K or λ normal or abnormal</th>
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</thead>
<tbody>
<tr>
<td>IFLC ≤ 100 mg/L</td>
<td>n = 23</td>
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<tr>
<td>n = 18</td>
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<tr>
<td>n = 11</td>
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3. LCO and OS myeloma at max response

163 patients with measurable disease at diagnosis (according to both assay (GILs) had serum samples available at max response. The absolute levels of dFLC were significantly higher on Freelite compared with Serum 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 ≥2vGPR on both assays.

4. Relationship between response by sFLC assessment and survival

Achieved sFLC response was correlated with improved survival in patients with ≥2vGPR for all serum and urine samples by both Freelite and Seraleit. An improved response was associated with longer OS and improved progression-free survival. However, the sFLC cut-off of 30 mg/L identified a smaller proportion of patients achieving ≥2vGPR, which was also associated with improved survival.

Conclusions

- The sFLC k: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 ≥2vGPR, according to either sFLC method, was associated with better overall and progression-free survival. Patients with ≥2vGPR 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 to dFLC level ≥20 mg/L identified for Seraleit. Relapse can be defined using a threshold of >30 mg/L increase in dFLC on Seraleit, 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 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 problems in receiving patient results. As a portable test, Seraleit 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, NSG and UC own shares intingham Health Ltd, who manufacture Serumite and MD schanes Ltd Ltd