Monitoring of light chain myeloma – time for a change

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Multiple myeloma, characterised in most instances by the excess production of monoclonal paraprotein or free light chains, has been traditionally monitored by serum (SPEP) and urine (UPEP) protein electrophoresis, respectively. Approximately 15% of patients with myeloma are light chain myeloma and <5% are non-secretory by these techniques. In fact, with the advent of the serum free light chain assay, approximately two-thirds of the non-secretory group have been found to secrete low levels of monoclonal free light chains that were not discernible by UPEP with immunofixation (Drayson, *et al.*, 2001). Monitoring response to treatment in these groups of patients with myeloma also requires the monoclonal component be "measurable", that is, to be of sufficient concentration that changes in consecutive levels post-treatment represent a significant change. Thus, we have arrived at the current International Myeloma Working Group hierarchical criteria for defining response to treatment (Kumar, *et al.*, 2016). A paraprotein must be >10 g/l to be measurable by SPEP. If not measurable by SPEP, then a 24-h urine specimen requires at least 200 mg of Bence Jones proteinuria (BJP) to be present. Serum FLC are recommended for monitoring myeloma only if disease is not measurable by SPEP or UPEP. Heaney *et al.* (2017), in this issue of the journal, provides evidence challenging this recommendation.

Heaney *et al.* have demonstrated, using data from the very large UK Myeloma IX and XI studies, that more patients with light chain myeloma and non-secretory myeloma can be monitored by serum FLC than by urine studies. They show that, while 20% of patients with light chain myeloma are not measureable by UPEP, >99% of such patients can be assessed by serum FLC. Of 60 patients with non-secretory myeloma, 38% could be monitored using the FLC assay. Importantly, response according to serum FLC assay was highly predictive of both progression-free and overall survival. Unfortunately, patients in the UK Myeloma IX and XI studies did not undergo 24-h UPEP measurements so there was no comparison with the current gold standard assessment. Nonetheless, this indicates the pragmatic difficulties of obtaining frequent 24-h urine specimens in clinical trials, let alone in routine clinical practice. The recent publication from Intergroupe Francophone du Myelome, where FLC determined response after three cycles predicted outcome in light chain myeloma and appeared superior to 24-h UPEP assessments, provides independent confirmation of these findings (Dejoie, *et al.*, 2016). These two studies presage a new standard in monitoring light chain myeloma and suggest there will be little role for UPEP in the majority of patients aside from confirmation of complete response.

To assess if this is the case requires understanding not only of these clinical trial results, but also of the assay methodologies. The 24-h urine collections have been the scourge of patients, clinicians and laboratory specimen reception officers alike. They are difficult to collect, have known inaccuracies and rely on methodologies to measure urine total protein and BJP that vary considerably between laboratories and fare poorly in laboratory quality assurance programmes (Jovanovich, *et al.*, 2010). Attempts to improve the pragmatic aspects by using "early morning" or "random" urine specimens and BJP measurement corrected for creatinine excretion lack clinical validity. The appeal of the serum FLC assay in this context is not difficult to understand. However, assays to measure serum FLC are not without their problems, as each patient's monoclonal FLC is a distinct protein and finding one assay to accurately measure this intrinsic variability has been notoriously difficult. The Freelite assay suffers from vulnerability to antigen excess and some analytical pitfalls (Tate, *et al.*, 2009). The Seralite assay, also the subject of this paper, is a newer assay which appears to have excellent laboratory characteristics but, being based on a cocktail of monoclonal antibodies, will, like all the FLC assays, fail to react with occasional patients' monoclonal light chain. All in all, however, the pragmatic advantage of measuring response with a single serum sample will overcome the analytical shortcomings of the various FLC assays. Is it time to dispense with UPEP in myeloma altogether? Probably not. In screening, UPEP will pick up the occasional patient not measureable by FLC assay and direct the laboratory to

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investigate discrepancies between serum FLC and urine BJP quantitation. In addition, the information gleaned from the relevant proportion of BJP and albumin to urine total protein gives an indication of underlying renal pathology due to glomerular or tubular dysfunction. It will only be the rare patient with light chain myeloma, however, that cannot be monitored by one of these FLC assays.

Another issue raised by this paper is the significant variation between the different FLC assays. While the Freelite and Seralite assays are compared in this paper, the N Latex assay is widely commercially available and there are new assays in development. From the report by Heaney *et al.* (2017) it is clear that absolute values vary considerably between assays even when performed in the same laboratory. For example, measurable disease is defined as involved FLC (iFLC) ≥100 mg/l for the Freelite assay whereas difference in FLC (dFLC) ≥20 mg/l was used for the Seralite assay. Similarly, percentage reductions, such as those involved in myeloma response criteria, also do not correlate precisely. As such, there is an urgent need to validate response criteria with each assay and to determine uniform criteria that can be applied to both clinical trials and routine monitoring. Alternative definitions of response may be required. Heaney *et al.* (2017) explore the interesting concept of whether complete response by FLC assay should be defined by a normalised FLC ratio or a normalised dFLC. This deserves further evaluation in other sample sets, although the dFLC criteria will be difficult to apply to patients with end stage renal failure where the median Freelite dFLC in patients without plasma cell diseases is 50 mg/l (Kennard, *et al.*, 2016). Harmonising the various FLC assays applies not only to monitoring myeloma but also in the diagnostic setting where "biomarkers of malignancy" are used to define symptomatic myeloma in need of therapy (Rajkumar, *et al.*, 2014). In this instance a Freelite-defined involved:uninvolved FLC ratio >100 has been clinically validated but data on alternate assays are lacking.

Despite these various limitations the paper by Heaney *et al.* (2017), together with that by Dejoie *et al.* (2016), indicate laboratory practice is changing. It suggests that the time has come for the serum FLC assay to be the preferred tool to monitor myeloma not measurable by SPEP. This will greatly facilitate the monitoring of myeloma, enable diagnosis of light chain escape, and leave only the occasional patient who requires 24-h UPEP monitoring.

References

Dejoie, T., Corre, J., Caillon, H., Hulin, C., Perrot, A., Caillot, D., et al. (2016) Serum free light chains, not urine specimens, should be used to evaluate response in light-chain multiple myeloma. *Blood*, **128**, 2941–2948.

Drayson, M., Tang, L.X., Drew, R., Mead, G.P., Carr-Smith, H. & Bradwell, A.R. (2001) Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. *Blood*, **97**, 2900–2902.

Heaney, J., Campbell, J., Griffin, A., Birtwistle, J., Shema, M., Child, T., Gregory, W.M., Cairns, D.A., Morgan, G., Jackson, G. & Drayson, M.T. (2017) Diagnosis and monitoring for light chain only and oligosecretory myeloma using serum free light chain tests. *British Journal of Haematology*, https://doi.org/10.1111/bjh.14753.

Jovanovich, S., Tate, J., Martin, H. & Wheatland, L. (2010) Performance of urinary bence jones protein measurement in clinical laboratories. *The Clinical Biochemist Reviews*, **31**, S30.

Kennard, A., Hawley, C., Tate, J., Klingberg, S., Pretorius, C., Hutchison, C. & Mollee, P. (2016) Comparison of Freelite and N Latex serum free light chain assays in subjects with end stage kidney disease on haemodialysis. *Clinical Chemistry and Laboratory Medicine*, **54**, 1045–1052.

Kumar, S., Paiva, B., Anderson, K.C., Durie, B., Landgren, O., Moreau, P., Munshi, N., Lonial, S., Blade, J., Mateos, M.V., Dimopoulos, M., Kastritis, E., Boccadoro, M., Orlowski, R., Goldschmidt, H., Spencer, A., Hou, J., Chng, W.J., Usmani, S.Z., Zamagni, E., Shimizu, K., Jagannath, S., Johnsen, H.E., Terpos, E., Reiman, A., Kyle, R.A., Sonneveld, P., Richardson, P.G., McCarthy, P., Ludwig, H., Chen, W., Cavo, M., Harousseau, J.L., Lentzsch, S., Hillengass, J., Palumbo, A., Orfao, A., Rajkumar, S.V., San Miguel, J. & Avet-Loiseau, H. (2016) International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *The Lancet Oncology*, **17**, e328–e346.

Rajkumar, S.V., Dimopoulos, M.A., Palumbo, A., Blade, J., Merlini, G., Mateos, M.V., Kumar, S., Hillengass, J., Kastritis, E., Richardson, P., Landgren, O., Paiva, B., Dispenzieri, A., Weiss, B., LeLeu, X., Zweegman, S., Lonial, S., Rosinol, L., Zamagni, E., Jagannath, S., Sezer, O., Kristinsson, S.Y., Caers, J., Usmani, S.Z., Lahuerta, J.J., Johnsen, H.E., Beksac, M., Cavo, M., Goldschmidt, H., Terpos, E., Kyle, R.A., Anderson, K.C., Durie, B.G. & San Miguel, J.F. (2014) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet Oncology*, **15**, e538–e548.

Tate, J., Bazeley, S., Sykes, S. & Mollee, P. (2009) Quantitative serum free light chain assay–analytical issues. *The Clinical Biochemist Reviews*, **30**, 131–140.