To the editor:

Sensitivity of serum free light chain measurement of residual disease in multiple myeloma patients

We were interested to read the communication from Singhal et al.[1] However, there is a misconception that serum free light chain (sFLC) measurement should provide the most sensitive measure of residual disease in all multiple myeloma patients. This appears to have arisen because normalization of the sFLC ratio has been included as one of the criteria necessary for achieving a "stringent complete response" in the proposed international response criteria.[2]

In fact, sFLC measurement provides a more sensitive measure of residual disease in some, but not all, myeloma patients. For patients whose tumors produce monoclonal light chains only (LCO), sFLC measurement will generally be more sensitive because (1) serum protein electrophoresis and immunofixation electrophoresis (IFE) are poor at detecting FLC, and (2) the sensitivity of urinalysis is restricted by the kidneys' capacity for reabsorbing and catabolizing FLC.[3] Retrospective studies showed sFLC measurement could have aided diagnosis and monitoring in 19 of 28 nonsecretory myeloma patients[4] and 224 of 224 LCO myeloma patients.[3] Twenty-six of 82 non-intensively treated LCO patients became IFE-negative in the urine, but 17 of these 26 patients had abnormal sFLC, indicating their maximum response was a partial response (PR) rather than complete response (CR).[3] Prospective study of 223 LCO patients in the MRC Myeloma IX trial showed 16 of 69 patients who had a PR by sFLC were IFE-negative in the urine. Furthermore, in 12 of 42 LCO patients, progression was detected by sFLC before their urine became IFE-positive.[5] In the same prospective study, light chain escape occurred in 5.3% IgG patients and 14.8% IgA patients.

However, for patients producing monoclonal intact immunoglobulins, the relative sensitivity of IFE and sFLC measurement will depend upon the quantities of protein being produced. It has previously been reported that approximately 5% of myeloma patients with monoclonal intact immunoglobulin produce no detectable monoclonal sFLC at presentation.[6,7] FLC ratios are only likely to be the more sensitive marker of residual disease in patients who have a relatively high production of FLC and certainly not in the approximately 5% of patients who apparently produce none.

A preliminary study by Kumar et al[8] has indicated that normalization of the sFLC ratio is a meaningful measure, associated with superior overall survival in myeloma patients achieving an IFE-negative response. For myeloma patients with monoclonal intact immunoglobulin and FLC, the persistence of abnormal sFLC, after becoming negative by IFE, could indicate the presence of tumor cells producing more FLC than intact immunoglobulin. Alternatively, it could result from the presence of a subclone of tumor cells producing FLCs only.[9] This latter phenomenon is more familiar when it is manifested at relapse as light chain escape.

Singhal and colleagues were right to highlight the more rapid falls shown by sFLC in response to successful therapy, which is due to the much shorter serum half-life of FLC (4-6 hours) compared with intact immunoglobulin (~ 6 days IgA, ~ 21 days IgG). However, it is wrong to conclude that normalization of the sFLC ratio will invariably predict an IFE-negative response.

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