Dial Traspl. 2009;**30(1)**:21-3

Diálisis y Trasplante

www.elsevier.es/dialisis

Ponencia

Free light chains in plasma cell disorders: measurement and therapeutic implications

Cadenas ligeras libres en los trastornos de las células plasmáticas: determinación e implicaciones terapéuticas

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INFORMACIÓN DEL ARTÍCULO

Historia del artículo:
Recibido el 30 de junio de 2008
Aceptado el 6 de octubre de 2008

Abstract

For 150 years, the presence of Bence Jones protein (immunoglobulin free light chains - FLCs) in the urine has been an important diagnostic marker for multiple myeloma MM. Indeed, it was the first cancer test and a century before any others. Over the last six years, however, interest in FLCs has undergone a renaissance. Development of serum tests for free kappa (κ) and free lambda (λ) has opened the door to new applications and increased their clinical importance.[1] By way of comparison, the management of diabetes mellitus was hugely improved when blood replaced urine for glucose analysis.

From a physiological viewpoint, blood tests for small molecular weight proteins have clear advantages over urine tests. Serum FLCs are rapidly cleared through the renal glomeruli with a serum half-life of 2-6 hours and are then metabolised in the proximal tubules of the nephrons. Under normal circumstances, little protein escapes to the urine so serum FLC concentrations have to increase many-fold before the absorption mechanisms are overwhelmed.[2] Hence, urinalysis is a fickle witness to changing FLC production. Conversion to a serum test provides clarity in assessing disease processes that were previously hidden from view.

Serum concentrations of FLCs are dependent upon the balance between production by plasma cells (and their progenitors) and renal clearance. When there is increased polyclonal immunoglobulin production and/or renal impairment, both κ and λ FLC concentrations can increase 30-40 fold. However, the relative concentration of κ to λ, i.e. the κ/λ ratio, remains unchanged. In contrast, tumours produce a monoclonal excess of only one of the light chain types, often with bone marrow suppression of the alternate light chain, so that κ/λ ratios become highly abnormal. Accurate measurement of κ/λ ratios underpins the utility of the serum FLC immunoassays and provides a numerical indicator of clonality. Urine κ/λ ratios are not as dependable because the non-tumour light chain production is too low to pass consistently through the nephrons. Electrophoretic tests can only be used to quantify the monoclonal light chain peak because they are not sensitive enough to identify the non-tumour FLC concentrations.

Early clinical studies with serum FLC tests were in patients with Bence Jones (light chain) MM. In studies, on 270 sera taken at the time of clinical presentation, highly abnormal serum FLC concentrations were found in every case.[3] Furthermore, during chemotherapy, urine tests frequently normalised while serum tests remained abnormal, indicating their increased sensitivity for residual disease. In this patient group, urinalysis can now be replaced by serum FLC tests. This is particularly helpful for frail, elderly patients because 24-hour urine samples are difficult to collect and results may be unreliable.

3-4% of patients with MM have so called nonsecretory disease. By definition, these patients have no monoclonal proteins by serum and urine electrophoretic tests. Nevertheless, several studies showed that FLC tests identified monoclonal proteins in 70-100% of patients. It is apparent that these patients' tumour cells produce small amounts of monoclonal protein. Their serum FLC concentrations are below the sensitivity of serum electrophoretic tests and below the threshold for clearance into the urine. Importantly, these patients can now be closely monitored by serum FLC tests rather than repeated bone marrow biopsies or whole body scans and can be entered into clinical trials of new treatments.

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Most patients with MM produce intact monoclonal immunoglobulins (IMIgs), yet FLCs are also abnormal in 95% of such patients at disease presentation. Interestingly, the serum concentrations of FLCs and IMIgs are not correlated (R < 0.02). Monoclonal serum FLCs are, therefore, independent markers of the disease process. This is of clinical importance when the tumour produces large amounts of FLCs and small amounts of IMIgs. Patients who are in apparent remission, as judged by study of their IMIgs, may still have residual disease as judged by elevated monoclonal FLCs. Using a similar argument, when these patients relapse, FLC concentrations may increase first. Free light chain, «breakthrough», is thought to occur in up to 15% of patients who relapse after modern, intensive treatment.

An additional feature of serum FLCs is that, in contrast to IMIgs, they are frequently nephrotoxic. In many patients with IMIgs the serum FLC concentrations are >1,000mg/L (50-100 times normal). This is characteristic of patients with IgD MM but is also apparent in 10-15% of IgG and IgA producing patients. The assays now allow assessment of the pre-renal load of monoclonal light chains. There is early evidence that in some patients, treatment should be aimed at normalising serum FLC concentrations in order to prevent renal damage.

One particularly interesting aspect of serum FLCs is their short half-life in the blood (κ 2-4 hours: λ 3-6 hours). This is approximately 100-200 times shorter than the 21-day half-life of IgG molecules. Hence, responses to treatment are seen in «real time.» This is apparent from the good correlation between bone marrow assessment of disease status and FLC concentrations but a poor correlation with serum IgG concentrations. Thus, FLC concentrations allow more rapid assessment of the effects of chemotherapy than monoclonal IgG. The impact of this is likely to be considerable. For instance, the resistance of patients to particular drugs or drug combinations can be observed quickly and alternative treatments chosen. The short half-life of FLCs also allows distinction between partial and complete tumour responses after one or two cycles of chemotherapy and before stem cell transplantation. The 21-day half-life of IgG hides complete responses whereas FLC analysis allows more accurate assessments.

Serum FLC tests are also having considerable impact in AL (primary) amyloidosis. Characteristically, light chain fibrils are deposited in various organs and tissues and directly lead to disease. The origin of the fibrils is monoclonal FLCs produced by a slowly growing clone of plasma cells. Concentrations are usually insufficient for measurement by serum electrophoretic tests. However, serum FLC assays provide quantification of the circulating fibril precursors in 90-95% of patients. Furthermore, the tests allow assessment of treatment responses and disease relapses that, in turn, correlate with survival. As stated by Dispenzieri et al., from The Mayo Clinic «The introduction of the serum immunoglobulin free light chain assay has revolutionised our ability to assess hematological responses in patients with low tumour burden». The combination of serum FLC and serum immunofixation electrophoresis (IFE) identified 109 of 110 patients at diagnosis in one study. The FLC analysis alone identified 91% of the patients while IFE identified only 69%, and urinalysis failed to identify the sole patient that was normal by both serum tests. A similar high sensitivity for the FLC assays has been found in light chain deposition disease.[4]

New national and international guidelines for the management of MM and AL amyloidosis include use of serum FLC measurements. Reduction of the κ/λ ratio to normal, alongside the IMIgs, is now the benchmark for complete serological responses to therapy in these and other monoclonal gammopathies. Additional emerging roles of serum FLC analysis are for assessing the risk of progression in individuals with monoclonal gammopathies of undetermined significance and asymptomatic MM. It seems that the low risk patients can be identified from normal FLC levels and can be reassured about their disease and may not need to be monitored on a long-term basis.

The high sensitivity of serum FLC immunoassays for tumour detection suggests they have a role in screening for B cell dyscrasias. Currently, symptomatic patients are assessed using serum and urine protein electrophoretic tests. Since urine is frequently unavailable, it is logical to add serum FLC analysis to current test protocols. Several studies have now shown that the combination of serum FLC analysis with serum protein electrophoretic analysis removes the need for urine tests for Bence Jones protein. Indeed, if the choice is between serum FLCs and serum or urine IFE, then FLC tests are more useful.[4] There is little, if any role for urine FLC analysis.

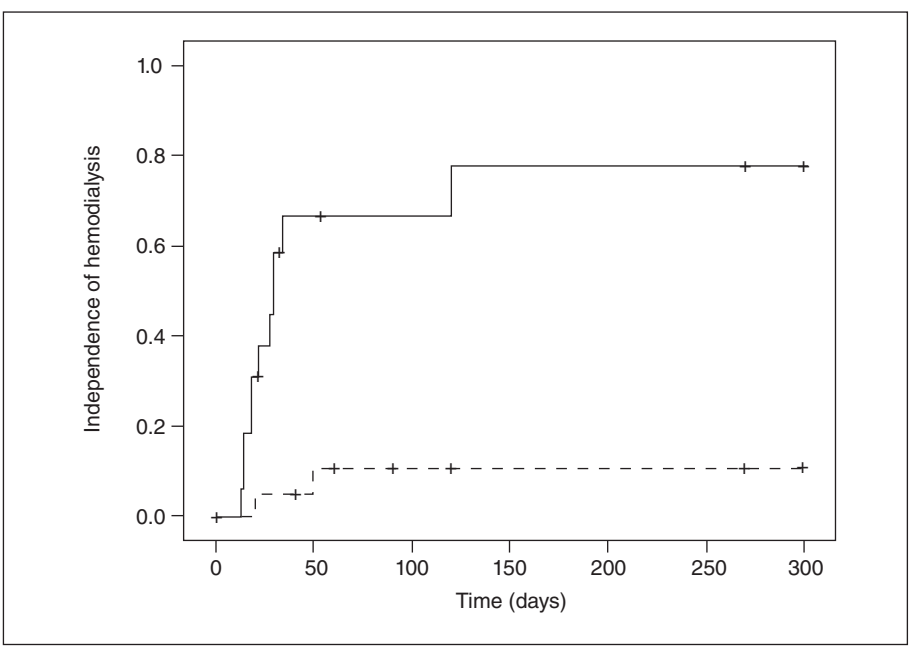

Figure 1. Comparison of renal recovery rates between patients who received FLC removal hemodialysis and historical case matched controls. Patients who received FLC removal HD (solid line) had a significantly higher chance of becoming independent of dialysis than patients treated conventionally (broken line); *P* < .0001.

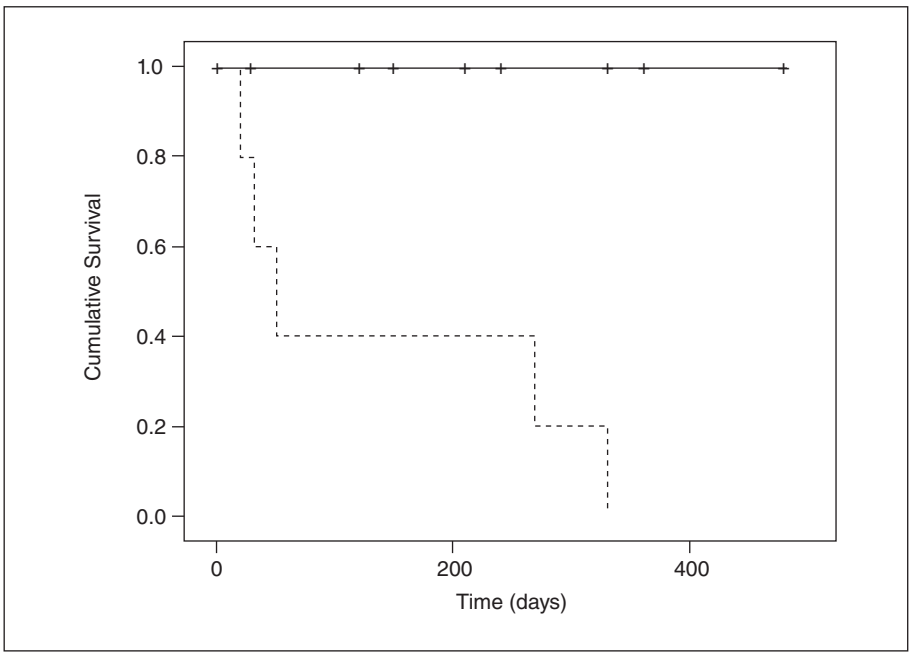

Figure 2. Cumulative survival of patients treated with FLC removal HD. Patients who developed infections requiring early withdrawal of chemotherapy and FLC removal hemodialysis (broken line) had a significantly reduced survival compared with patients who received uninterrupted treatment (solid line); $P < .002$.

Finally, there was a recent report documenting recovery of 3 patients with myeloma kidney (cast nephropathy) and dialysis dependent acute renal failure following FLC removal by high cut-off hemodialysis.[5] A subsequent report of 17 patients showed that 12 (70%) became independent of dialysis, versus 2/18 in a case matched control group (11%, $P < .0001$), which is typical from historical studies (fig. 1).[6] The 12 patients who recovered renal function achieved a median sustained serum FLC reduction of 86% during treatment (50-93%). Their median time to independence of dialysis was 24 days (13-50 days) with an estimated mean GFR at three months of 44mls/min/1.73m^2 (GFR: 29-60). All patients who recovered renal function were alive 20 months after the commencement of the study, whereas the 5 who did not recover renal function all died, with a median survival of less than six months ($P < .02$) (fig. 2).

In summary, serum FLC tests are assuming an increasing role in the detection and monitoring of patients with monoclonal gammopathies. This new approach is bringing significant therapeutic benefits to the many patients with these serious diseases.

Acknowledgments

This manuscript has been published by the Mikel partnership of The Binding Site Conde (Spain).

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