ELSEVIER DOYMA

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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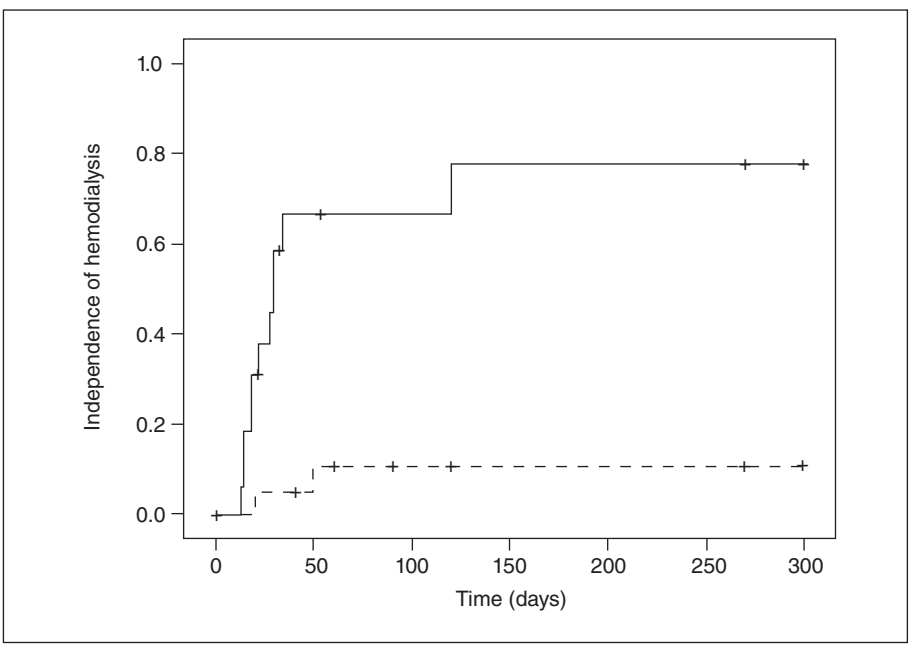
Independence of hemodialysis
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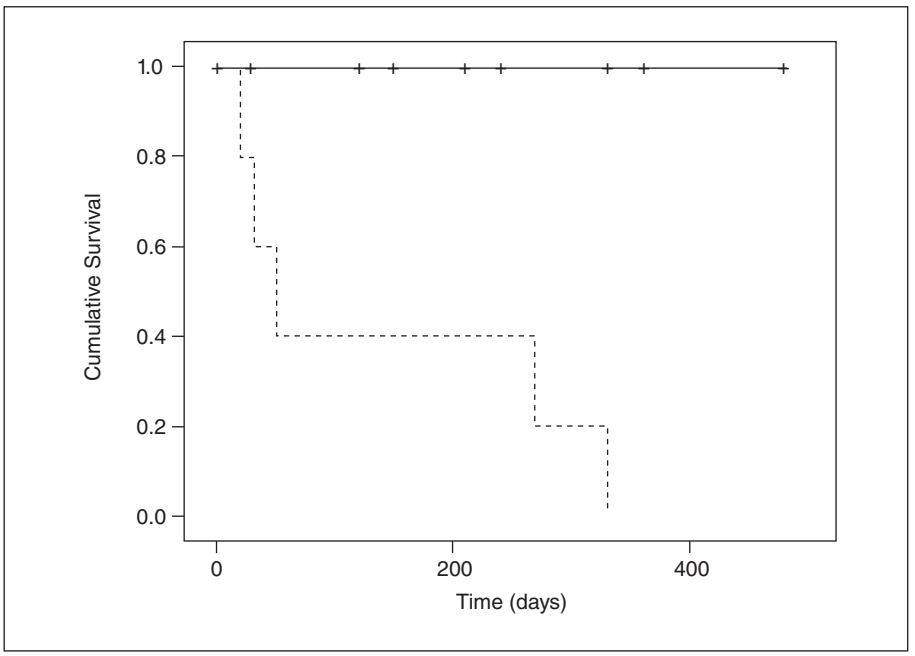
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
300
Time (days)


1.0
0.8
0.6
0.4
0.2
0.0
Cumulative Survival
0
200
400
Time (days)