Brief report

Abnormal serum free light chain ratio in patients with multiple myeloma in complete remission has strong association with the presence of oligoclonal bands: implications for stringent complete remission definition

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The prevalence of an abnormal serum free light chain (FLC) ratio in 34 patients with multiple myeloma in complete remission (CR) after hematopoietic stem cell transplantation was studied. Fourteen of 34 patients (41.2%) showed an abnormal FLC ratio. The frequency of abnormal FLC ratio in patients with or without oligoclonal bands was 72.7% versus 26%, respectively (P = .023). The median value of FLC ratio was 2.55 (95% confidence interval, 1.89-3.20) in patients with oligoclonal bands versus 0.87 (95% confidence interval, 0.70-1.04) for those with no oligoclonal bands (P = .011). This is the first report showing that the presence of oligoclonal bands in patients with multiple myeloma in CR frequently results in an abnormal FLC ratio. Because an oligoclonal immune response is associated with a good outcome, our results question the current definition of stringent CR and support that the prognostic impact of oligoclonal bands should be also assessed on multivariate analysis. (Blood. 2009;114:4954-4956)

Introduction

Complete remission (CR) in multiple myeloma (MM) is defined by the absence of the original monoclonal protein in both serum and urine immunofixation (IFE).1 The measurement of serum free light chains (FLCs) can potentially allow the detection of levels of free κ and λ chains below the IFE threshold.2 Theoretically, this assay could help to identify groups of patients in CR with different risk of progression. In this regard, the International Myeloma Working Group (IMWG) has recently proposed the so-called Uniform Response Criteria, incorporating a normal FLC ratio (0.26:1.65) to fulfill the stringent complete response (sCR).3 In addition to negative IFE in serum and urine plus less than 5% clonal bone marrow plasma cells. However, there are limited data on the prognostic significance of sCR.2 Interestingly, 10% to 33% of patients with MM in CR have monoclonal or oligoclonal bands, a fact associated with a favorable outcome.4,5 These oligoclonal bands result from a robust humoral immune response to therapy and are different and unrelated to the baseline myeloma protein. The aim of this study was to determine the prevalence of abnormal FLC ratio in patients with MM in CR after stem cell transplantation and to establish its possible relationship with the presence of oligoclonal bands.

Methods

Thirty-four patients (16 male/18 female; median age, 50 years) with MM who reached CR after hematopoietic stem cell transplantation (26 autologous and 8 allogeneic) were studied. The study was approved by the Ethics Committee of Hospital Clinic of Barcelona. The diagnosis of MM was established according to the criteria of the Chronic Leukemia-Myeloma Task Force.6 CR was defined according to European Blood and Marrow Transplantation criteria.1 Thus, all patients had a negative serum and urine IFE for the original monoclonal myeloma protein and less than 5% bone marrow plasma cells. The median follow-up in CR was 5 years (range, 1-23.2 years). The main characteristics of the patients are detailed in Table 1.

An oligoclonal band was defined by a serum and/or urine IFE different either in heavy and/or light chain component from the original monoclonal protein. The serum FLC measurement (FREELITE assay; Binding Site Ltd) was performed by immune nephelometry, and serum FLC ratio κ/λ was determined. FREELITE assays were kindly provided by Binding Site Ltd. Statistical tests were performed with SPSS software 14.0 for Windows. Categorical variables were contrasted by Fisher exact test and median differences by Mann-Whitney U test.

Results and discussion

Serum and/or urine oligoclonal bands were observed in 14 of the 34 patients (41.2%). The characteristics of this subgroup of patients are shown in Table 2. The isotype distribution of the original myeloma protein and the monoclonal and oligoclonal bands for patients who developed new immunoglobulins is shown in Table 2. Eight patients (57.1%) presented a fluctuating oligoclonal pattern during their follow-up, whereas the remainder showed a single oligoclonal immunoglobulin. Eleven of the 34 patients (32.4%) had an abnormal serum FLC κ/λ ratio, being in all cases higher than the upper normal limit, which indicates an overproduction of κ light chains. This discordance between the light chain involved in the oligoclonal IFE pattern and light


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chain in excess in FLC ratio has been previously reported, and it most probably reflects the degree of immune reconstitution rather than the result of a specific light chain clonal production. IFE oligoclonal bands were detected in 8 of the 11 patients with an abnormal FLC ratio (72.7%) versus 6 of 23 (26%) with a normal serum FLC ratio ($P = .023$). Moreover, the median value of serum FLC ratio was higher in patients with IFE oligoclonal bands (2.55; 95% confidence interval, 1.89-3.20 versus 0.87; 95% confidence interval 0.70-1.04; $P = .011$). CD4 levels at 4 months after transplantation were available in 14 patients. Although the median value was higher in patients with abnormal FLC ratio (418/mL vs 329/mL) and in those with oligoclonal bands (417/mL vs 294/mL), the differences did not reach statistical significance.

The emergence of oligoclonal bands was first recognized after autologous stem cell transplantation (ASCT). Thus, in a series from the University of Arkansas, 10% of the patients with MM who underwent ASCT showed IFE oligoclonal bands or isotype switch. The presence of ASIPs was associated with a significantly higher CR rate (71% vs 23%). It is a general thought that oligoclonal bands are transient. In the University of Arkansas series, the median duration of IFE oligoclonal bands was 7 months (range, 1-22 months). However, in our series, the oligoclonal bands lasted from 0.7 to 9.4 years and persisted during all follow-up in all patients except in one who relapsed (Table 2). Our results agree and are supported with the findings of Mark et al, who showed that IFE oligoclonal bands fluctuated and persisted for years. The emergence of serum oligoclonal bands reflects a robust humoral immune response and consequently an immune system reconstitution that can be achieved after either HDT/SCT or highly effective nonmyeloablative therapy with novel agents. There was no available information regarding the incidence of sCR in patients with or without oligoclonal bands in the aforementioned series. Kumar et al reported in abstract form that sCR was an independent survival predictor in patients with MM and negative IFE after ASCT, but no information was given concerning the presence or absence of IFE oligoclonal bands.

Higher pretransplantation and posttransplantation CR rate is being reported with the incorporation of novel agents in induction pretransplantation regimen. Similarly, in patients not eligible for ASCT, new combination regimens melphalan, prednisone, and thalidomide, or bortezomib, melphalan, prednisone, and lenalidomide, or lenalidomide/dexamethasone are resulting in an unprecedented CR rate of 15%, 30%, 24%, and 24%, respectively. As Mark et al reported, it is very probable that the emergence of IFE oligoclonal bands in patients in CR after treatment with these novel agents is considerable. Indeed, in our experience, the prevalence of oligoclonal bands in 31 patients in CR after standard-dose therapy is significantly higher when including with a significantly higher CR rate (67% vs 37%) and with significantly longer event-free survival and overall survival. Mark et al have recently reported that 33% of patients treated with clarithromycin, lenalidomide, and dexamethasone developed what they termed atypical serum IFE patterns (ASIPs) consisting of the emergence of monoclonal and oligoclonal immunoglobulins unrelated to the original monoclonal protein. The presence of ASIPs was associated with a significantly higher CR rate (71% vs 23%).

<table>
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<th>Patient no.</th>
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<th>Allogeneic transplantation</th>
<th>Original M-spike</th>
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Primary chemotherapy: (1) VBCMP/VBAD; (2) bortezomib/dexamethasone; (3) VAD; (4) thalidomide/dexamethasone; and (5) bortezomib/thalidomide/dexamethasone.

*Tandem autologous/allogeneic transplantation.

†MM and associated systemic amyloidosis: high-dose therapy with no previous induction.

‡With the same original isotype but different migration pattern in serum immunofixation.

§Abnormal ratio.
novel drugs than with cytotoxic agents (51.7% [8/14] vs 11.8% [2/17]; P = .009; C.F.d.L., M.T.C., N. Tovar, L.R., J.L.A., J.Y., J.B., unpublished observation, August 2009). According to our results, the presence of oligoclonal bands frequently results in an abnormal serum FLC ratio. The IMWG CR, as currently defined, does not distinguish between patients with or without IFE oligoclonal bands in patients who are negative for their original monoclonal protein. In addition, although the recent IMWG guidelines for serum FLC analysis recommend the use of serum FLC k/a ratio to document sCR, the prognostic impact of sCR versus non-sCR has not yet been validated.2 Our results support that, when the prognostic impact of sCR versus CR is formally validated, the analysis should also address the presence of IFE oligoclonal bands.

In conclusion, this is the first report showing that the presence of IFE oligoclonal bands in patients with MM in CR frequently results in an abnormal serum FLC ratio. Our results question the current definition of sCR and support that its possible prognostic relevance should be studied, taking into account the presence of ASIPs in a multivariate analysis.

References


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Authorship

Contribution: C.F.d.L. and J.B. designed the research, collected and analyzed the data, performed statistical analysis, and wrote and reviewed the paper; M.T.C., L.R., and M.R. treated the patients, collected data, and reviewed the paper; and M.E., J.L.A., X.F., and J.Y. performed the assays and reviewed and approved the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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