To the editor:

Questionable role of free light chain assay ratio to determine stringent complete remission in multiple myeloma patients

We read with interest the Brief Report by Fernandez de Larrera investigating the role of abnormal serum free light chain ration in patients with complete remission.[1] The qualitative assay for free light chain has been reported to be sensitive and specific for detecting and monitoring diseases caused by monoclonal gammopathies, such as multiple myeloma.[2] More recently, the International Myeloma Working Group proposed uniform response criteria including a new definition of stringent complete remission (sCR). The definition of sCR requires absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence and normalization of free light chain ratio in serum.[3] More recently, the International Myeloma Working Group also published guidelines for serum free light chain analysis in multiple myeloma and related disorders.[4] Here, it was recommended to be performed in all patients who achieved a complete remission with negative immunofixation a serum-free light chain assay to determine a "stringent CR." However, the authors also pointed out that there were no data yet to document that a complete response, with or without a free light chain ratio criterion, is prognostic for progression-free survival or overall survival.

In a small study monitoring sequential serum-free light chain assay in 26 patients with negative immunofixation, we observed that normalization of the free light chain ratio preceded the occurrence of immunofixation negativity by approximately 3 months, which is probably due to the shorter serum half-life in comparison with intact immunoglobulin.[5]

Here, we evaluate the value of free light chain assay to determine sCR by monitoring 52 patients with multiple myeloma who achieved complete remission between January 2003 and December 2008 according European Group for Blood and Marrow Transplantation criteria[6] with negative immunofixation in serum and urine for the original monoclonal myeloma protein. Free light chain measurements were performed with the commercially available Freelite Kit (Binding Site). Because of the aforementioned shorter half-life of free light chain assay ratio,[5] patients were included only if the complete remission remained stable for at least 3 months. The comparison between immunofixation and free light chain ratio was performed at least 6 weeks after immunofixation becomes negative for the first time. The patients had intact immunoglobulin (n = 47) or light chain immunoglobulin (n = 5) at time of diagnosis. The remission status was determined either after allogeneic (n = 45) or autologous (n = 3) stem cell transplantation or after conventional bortezomib- or lenalidomide-containing chemotherapy (n = 4).

These 52 patients achieved complete remission according to the European Group for Blood and Marrow Transplantation criteria with negative immunofixation for at least 3 months. Fifty-one of 52 patients (98%) had a normal free light chain κ/λ ratio. In contrast to the study of de Larrea, none of the patient with oligoclonal bands in immunofixation (n = 13) had abnormal free light chain κ/λ ratio. However, in a subgroup of patients (n = 10) who relapsed during follow-up from complete remission sequential monitoring of immunofixation and free light assay was performed as recently described.[5] In 9 of 10 patients a free light chain ratio became abnormal at a median of 90 days before immunofixation became positive. These results confirm that the free light chain assay ratio is, due to its shorter half-life, a useful marker for faster detection of remission or progression in myeloma patients, but these results do not support additional value of free light chain ratio to determine the depth of remission in immunofixation-negative patients. More sensitive methods such as imunophenotyping analysis by fluorescence-activated cell sorting or molecular primer should be used to determine depth of complete remission because these methods have shown relevant clinical impact.[7-9]

Nicolaus Kröger
Clinic for Stem Cell Transplantation, University Medical Center Eppendorf, Hamburg, Germany

Svetlana Asenova
Clinic for Stem Cell Transplantation, University Medical Center Eppendorf, Hamburg, Germany

Andreas Gerritzen
Medical Laboratory, Bremen, Germany

Ulrike Bacher
Clinic for Stem Cell Transplantation, University Medical Center Eppendorf, Hamburg, Germany

Axel Zander
Clinic for Stem Cell Transplantation, University Medical Center Eppendorf, Hamburg, Germany

Contribution: N.K. designed the study, analyzed data, and wrote the letter; S.A. collected and analyzed data; A.G. performed free light assay; U.B. and A.Z. analyzed data; and all authors approved the letter.

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Correspondence: Prof Dr med Nicolaus Kröger, Department for Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Martinistr 52, D-20246 Hamburg, Germany; e-mail: nkroeger@uke.uni-hamburg.de.

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Response

Free light chain assay and stringent complete remission in multiple myeloma: more questions than answers

We appreciated the comments by Kröger et al on our article and we have read with interest their experience with free light chain (FLC) measurements in 52 patients with multiple myeloma (MM) in complete remission (CR) after allogeneic stem cell transplantation (Allo-SCT; n = 45), autologous stem cell transplantation (ASCT; n = 3) or conventional bortezomib- or lenalidomide-based therapy (n = 4). The high rate of stringent CR (sCR), with 51 of 52 (98%) of the patients achieving a normal FLC κ/λ ratio, is surprising. Moreover, none of their 13 patients with oligoclonal bands had an abnormal FLC κ/λ ratio, which contrasts with our results.[1]

The differences between the 2 studies may be explained by the nature of the treatments and the timing of light chain measurement. In the series by Kröger et al, 87% of the patients had achieved CR after Allo-SCT, whereas in our study 76.5% were in CR after ASCT. It is very likely that the immune reconstitution could be different and more delayed after the allogeneic procedure. Of note, in Kröger's study, the free light chains were measured in patients who had been in stable CR for a minimum of only 3 months and at least 6 weeks from the first negative immunofixation electrophoresis. On the contrary, in our series, median duration of the CR was 5 years (range, 1-23.2 years), and median time of oligoclonal band appearance after allogeneic or autologous SCT was 6 months (range, 2-53 months). It is conceivable, therefore, that in those patients with long-lasting responses after high-dose therapy/SCT the robust immune reconstitution would result in the presence of oligoclonal bands and an abnormal FLC ratio, due to a kappa light chain overproduction. In fact, there is a general thought that these oligoclonal bands are transient.[2] However, in our 14 patients the duration of oligoclonal bands ranged from 0.7 to 9.4 years and persisted in all of them except in the only one who relapsed, in keeping with a recent report by Mark et al.[3]

There are still many important unsolved issues concerning FLC measurements and sCR in MM. (1) At what time could the FLC assay be more informative (early or after a certain duration of the CR)? (2) Does the frequency of sCR vary depending on the type of treatment? (3) Is the meaning of sCR different after conventional chemotherapy, ASCT, or Allo-SCT? (4) What is the significance of an abnormal FLC ratio in patients with oligoclonal bands? (5) Is sCR of real prognostic value and, if so, in what population of patients?

Finally, we agree completely with Kröger et al that, with the current therapeutic approaches for MM as well as the availability of novel laboratory technologies, the achievement of serologic CR should no longer be the ultimate endpoint. The recent results on the prognostic impact of minimal residual disease studies by multiparameter flow cytometry[4] and by molecular quantitative reverse transcription–polymerase chain reaction[5] are important steps forward that can be crucial to determining for how long beyond serologic CR additional treatment is needed.

Carlos Fernández de Larrea
Department of Hematology, Hospital Clínic, Barcelona and Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain

María Teresa Cibeira
Department of Hematology, Hospital Clínic, Barcelona and Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain

Montserrat Elena
Department of Biochemistry, Hospital Clínic, Barcelona and Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain

Juan Ignacio Arostegui
Department of Immunology, Hospital Clínic, Barcelona and Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain

Laura Rosiñol
Department of Hematology, Hospital Clínic, Barcelona and Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain

Montserrat Rovira
Department of Hematology, Hospital Clínic, Barcelona and Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain

Xavier Filella
Department of Biochemistry, Hospital Clínic, Barcelona and Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain

Jordi Yagüe
Department of Immunology, Hospital Clínic, Barcelona and Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain

Joan Bladé
Department of Hematology, Hospital Clínic, Barcelona and Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain

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Correspondence: Joan Bladé, MD, Servei d'Hematologia, Hospital Clínic de Barcelona, Villarroel 170, 08036 Barcelona, Spain; e-mail: jblade@clinic.ub.es.

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