Comparative Response Assessment by Serum Immunoglobulin M M-Protein and Total Serum Immunoglobulin M After Treatment of Patients With Waldenström Macroglobulinemia

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Abstract

Serum immunoglobulin (Ig) M monoclonal protein determined by electrophoresis (sIgM-MP) and total serum IgM (sIgM) by nephelometry are widely used for response assessment in Waldenström macroglobulinemia (WM), although have not been compared for predicting changes in underlying disease burden. We, therefore, compared these serum markers with changes in bone marrow (BM) and extramedullary disease for 73 patients who were rituximab naive and treated with a rituximab-containing regimen. By linear regression analysis, reductions in sIgM-MP and sIgM showed moderate correlation with BM disease involvement ($r = 0.4051$ and $r = 0.4490$, respectively), and did not differ from one another as estimators of BM disease response ($P = .3745$). Neither sIgM-MP nor sIgM showed a strong correlation with BM disease response in patients with low (<1000 mg/dL) or high (>5000 mg/dL) IgM levels and extramedullary disease response. sIgM-MP and sIgM, therefore, are comparable response markers in WM. Development of newer, more accurate surrogate response markers are needed to better delineate treatment outcomes in patients with WM and with low or high IgM levels, and extramedullary disease.

Introduction

Waldenström macroglobulinemia (WM) is a B-cell lymphoproliferative disease that is characterized by lymphoplasmacytic cell infiltration of the bone marrow (BM) and the presence of an immunoglobulin (Ig) M monoclonal gammopathy; it is classified as a lymphoplasmacytic lymphoma by the World Health Organization and the Revised European-American Lymphoma classification systems.[1-4] The presence of extramedullary disease, including adenopathy and splenomegaly, is commonly observed in WM.[5] Changes in sIgM-MP and sIgM levels have been used as surrogate response markers after WM treatment,[6-8] and consensus response criteria were recently updated to allow use of either sIgM-MP or sIgM in assessing treatment outcome in WM.[9] Because the ability for these markers to reflect changes in underlying BM disease burden has not been formally compared, these comparative studies were undertaken to clarify which surrogate marker (sIgM-MP vs. sIgM) more accurately reflects changes in BM and extramedullary disease burden after treatment of patients with WM.

Patients and Methods

Seventy-three patients who were rituximab naive who underwent treatment on a clinical study with a rituximab-based therapy and for whom serial sIgM-MP, sIgM, BM, and computed tomography scans of chest, abdomen, and pelvis were available were included in this study.[10] Treatment consisted of bortezomib with rituximab and dexamethasone (n = 25), cyclophosphamide with rituximab and steroids (n = 13), immunomodulatory drug (IMID)-based treatment with rituximab (n = 13), nucleoside analog with rituximab (n = 16), and rituximab monotherapy (n = 6). The patients received a median 6 cycles (range, 2-8) of rituximab induction therapy. The median age of patients was 61 years (range, 44-84 years), and 52% (71.2%) were previously untreated. Baseline median values were as follows: sIgM, 3960 mg/dL (range, 454-12,400 mg/dL); sIgM-MP, 2.55 g/dL (range 0.28-4.67 g/dL); and BM disease involvement was 60% (range, 5%-95%). Five (6.8%) patients had sIgM levels <1000 mg/dL, and 23 (31.5%) patients had sIgM levels >5000 mg/dL. Thirty-nine (52.7%) patients demonstrated lymphadenopathy and/or splenomegaly on baseline computed tomographies of the chest, abdomen, and pelvis. Total sIgM-MP was determined by pro-

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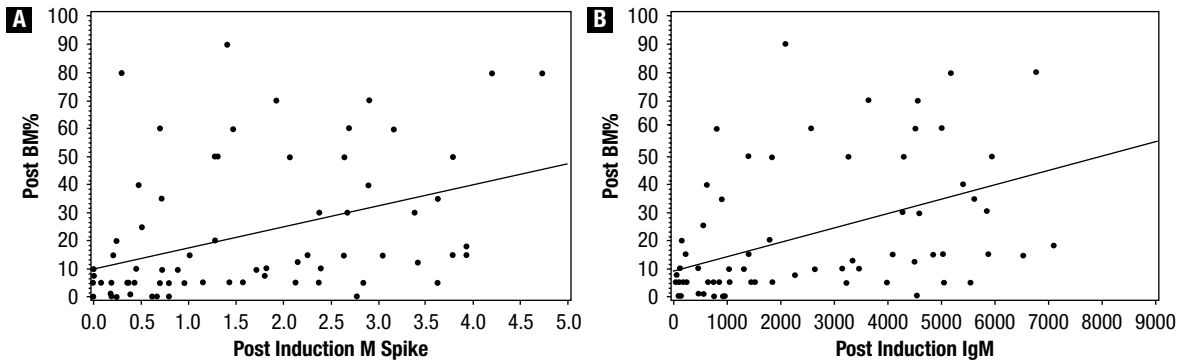
Figure 1 Linear Regression Analysis Comparing Postinduction sIgM-MP (A) and sIgM (B) With Postinduction WM Disease Involvement



tein electrophoresis and total sIgM by nephelometry at a Clinical Laboratory Improvement Amendments (CLIA)-certified clinical laboratory (Brigham and Women's Hospital, Boston, MA). Baseline and posttreatment sIgM-MP and sIgM levels, BM biopsies, and computed tomographies were reviewed for this analysis. Linear regression studies were performed for sIgM-MP and sIgM against BM involvement. Subset analyses were performed for patients with baseline sIgM levels below 1000 mg/dL (n = 5) and above 5000 mg/dL (n = 23) as well as for patients with extramedullary disease (n = 39). An r to z transformation was performed to calculate a value of z that will assess the significance of the difference between correlation coefficients.

Results

After induction therapy, median sIgM-MP declined from 2.55 to 1.28 g/dL (range, 0-4.73 g/dL; $P < .0001$), median sIgM declined from 3960 to 1800 mg/dL (range 36-7060 mg/dL; $P < .0001$), and median BM involvement declined from 60% to 10% (range, 0%-90%; $P < .0001$) for all patients. Among the 39 patients with baseline extramedullary disease, improvements in adenopathy and/or splenomegaly were documented for 18 (46.2%) patients, no change in 14 (36.0%) patients, and increased in 7 (17.9%) patients. When using modified consensus response criteria,[8] the overall (minor response or better) response rate for these patients was 98.6%, including complete response (10.9%), very good partial response (4.1%), partial response (60.3%), minor response (23.3%), and stable disease (1.4%).

By linear regression analysis, reductions in sIgM-MP and sIgM correlated with corresponding decreases in BM disease involvement, although both associations were moderate ($r = 0.4051$ [$P = .0004$] and $r = 0.4490$ [$P < .0001$], respectively) (Figure 1). To assess the significance of the difference between sIgM-MP and sIgM for correlation with BM disease response, an r to z transformation was performed, which demonstrated that sIgM-MP and sIgM were not significantly different predictors for BM disease response ($P = .3745$). Neither sIgM-MP or sIgM were good estimators of BM response in patients with baseline sIgM levels <1000 mg/dL ($r = 0.4323$ [$P = .4672$] for sIgM-MP, and $r = .6029$ [$P = 0.2815$] for sIgM) or in patients with baseline sIgM levels >5000 mg/dL ($r = 0.1749$ [$P = .4246$] for sIgM-MP, $r = .2760$ [$P = 0.2022$] for sIgM). For the 39 patients with baseline extramedullary disease, neither sIgM-MP nor sIgM showed a significant correlation with responses in adenopathy and/or splenomegaly ($r = 0.2298$ [$P = .23947$] for sIgM-MP, and $r = 0.3239$ [$P = .0927$] for sIgM; data not shown).

Discussion

We undertook this study to clarify which serum marker (sIgM-MP vs. sIgM) more accurately reflects changes in BM and extramedullary disease burden after treatment of patients with WM. Among 356 previously untreated patients, Treon[5] observed that sIgM levels did not directly correlate with underlying BM disease burden, although the relationship of sIgM-MP or sIgM after BM treatment response was not addressed in that publication.

In this study, we observed that sIgM-MP and sIgM showed similar levels of correlation with changes in BM disease response in patients with WM responding to therapy. Overall, sIgM-MP and sIgM showed a moderate level of correlation with BM disease burden and were particularly poor in predicting changes in BM disease burden in patients with low (<1000 mg/dL) or high (>5000 mg/dL) sIgM, and extramedullary disease response. Technical difficulties due to paraprotein aggregation, migration of immunoglobulins to the beta region of the immunofixation gel, and the presence of IgM multimers have been raised as limitation to accurate estimation of sIgM-MP in patients with WM,[11] whereas, at higher IgM levels, sIgM estimation by nephelometry can vary with a bias for overestimation.[5,12] Although the current WM response assessment criteria have been updated to permit categorical response assessment and progression by use of either sIgM-MP or sIgM levels, these studies point to the limitation of these serum markers for assessing WM disease response and highlight the need for more accurate response tools in WM. The recent discovery of MYD88 L265P as a widely expressed somatic mutation in WM[13] may permit use of MYD88 L265P copy number changes by real-time allele-specific polymerase chain reaction for tu-

mor burden assessment in patients with WM, as recently reported by Xu et al.[14]

In summary, sIgM-MP and sIgM show similar capacity to predict BM response outcome in WM patients, though their correlation to underlying BM disease burden is moderate, and particularly poor in patients with low or high baseline sIgM levels, and extramedullary disease.

Disclosure

The authors have stated that they have no conflicts of interest.

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