Monoclonal Gammopathy of Undetermined Significance and Multiple Myeloma

Robert A. Kyle, MD; S. Vincent Rajkumar, MD

In this issue of JAMA Oncology, Sigurдардóttir et al1 raise an important point concerning the effect of diagnosis and follow-up of patients with monoclonal (M) gammopathy of undetermined significance (MGUS) on the survival of multiple myeloma (MM). In their study of 14,798 patients with MM diagnosed in Sweden from 1976 to 2005, 394 (2.7%) had a previously recognized MGUS. In an important finding, patients who developed MM and who had a previously recognized MGUS had a higher overall survival (median survival, 2.8 years) than those patients with MM in whom MGUS had not previously been recognized (median survival, 2.1 years). The findings suggest a survival benefit for those patients with MM who had a previously recognized MGUS. The results of this study are similar to those of a recent report by Go et al2 that also found that outcome of MM was better in patients with a prior diagnosis of MGUS compared with those diagnosed without a history of MGUS. However, the study suffers from the same drawbacks in that the results provide associations but cannot be used to determine causal relationships or to make public health decisions.

MGUS is characterized by the presence of a serum M-protein concentration lower than 3 g/dL, the presence of fewer than 10% M-plasma cells in the bone marrow, and the absence of end-organ damage, such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder. The diagnosis and classification of MGUS, MM, and related disorders has been recently updated by the International Myeloma Working Group.

In invited commentary, Kyle and Rajkumar discuss the implications of these studies on the management of patients with MGUS and MM.


It has been shown that virtually all patients with MM have a preceding MGUS. At least 15% of patients with symptomatic MM produce no heavy chain (IgG, IgA, IgD, or IgE), and only M light chains (κ or λ chains) are produced. In these patients, the amount of light chains may progress to light-chain smoldering MM, which is characterized by the excretion of a urinary light-chain M-protein concentration of at least 0.5 g/24 h and/or more than 10% M-plasma cells in the bone marrow but without CRAB features.

The central premise of the article by Sigurdardottir et al1 is that the reason for better outcome in patients with MM with known MGUS is due to the probability that such patients were followed up closely and this led to a timely diagnosis of MM and fewer complications. It cannot be determined whether MM patients with a known MGUS in the Icelandic study1 were followed more closely than those in whom a MGUS was not recognized, and hence it is difficult to attribute a causal relationship between follow-up and better prognosis. Other factors that may play a role include the possibility that MGUS is recognized clinically, is biologically different, and may be more long-standing than MGUS that is not recognized. Multiple myeloma is a clinical diagnosis, and the timing at which a patient is identified as having MM is subject to lead time bias in patients known to have MGUS. Second, the presence of comorbidities in those patients with MM with a known MGUS (which was the reason testing for MGUS was done in the first place) makes such patients more likely to seek medical care and thus be followed more closely before development of symptomatic MM. The occurrence of autoimmune disorders, infectious diseases, ischemic heart disease, congestive heart failure, cerebrovascular accidents, and renal disease were more common in the MM patients with prior recognition of MGUS because of closer follow-up, and this may have contributed to the longer survival of those with a previously recognized MGUS. This would have occurred regardless of the diagnosis of MGUS. Furthermore, the median survival of this MM cohort was less than 3 years compared with more than 5 years currently. Finally, we need to be careful about attributing changes in outcome as being secondary to better follow-up. Such data need to come from randomized clinical trials.

It is interesting to note that patients with a lower M-protein concentration were found to have shorter survival following the diagnosis of MM. However, as noted, it is not possible from the present study to determine any causal relationship between close follow-up or lack thereof of these patients and outcome of MM. For example, patients with small M spikes may have more light-chain excretion and higher prevalence of light-chain MM. Such patients are also at risk of AL amyloidosis in addition to MM. We feel that data from this article cannot be used to dismiss the risk-adapted approach to follow-up of MGUS recommended by the IMWG (and the Mayo Clinic). The IMWG recommendation for a risk-stratified approach to follow-up of MGUS is based on data indicating that the absolute risk of progression over a 20-year follow-up of a patient with low-risk MGUS is only 2% when competing causes of death are accounted for. This risk-stratification model used a cutoff of 1.5 g/dL for M-protein concentration; a lower threshold of 0.5 g/dL would result in an even lower absolute risk of progression. It is clear that public health attempts to reduce the probability of an event (eg, MM) and the prognosis of that event should always take into account the baseline risk. Furthermore, the IMWG risk stratification does not rely solely on M-protein concentration alone but also requires free light-chain ratio and M-protein type to be factored in.

This study indirectly suggests that knowledge of a prior MGUS may lead to better survival, but the mechanisms by which this occurs are not clear. We need prospective studies to address the value of follow-up in MGUS and the optimal approach to such follow-up. The risk-adapted approach is a compromise that ensures that scarce resources are focused on the patients most likely to benefit. We also need studies to address the question of the possible merits of screening for the presence of MGUS in a normal, older population. The cost, inconvenience, and anxiety produced by the awareness of potential progression of a recognized MGUS, as well as the low absolute risk of progression (0.5%-1% per year), probably over-ride the possible potential benefit of screening for MGUS.

REFERENCES