


21. Therneau T. A Package for Survival Analysis in S. R package version 2.3.7-2.


Monoclonal Gammopathy of Undetermined Significance and Multiple Myeloma

(ImWG). It has been shown that virtually all patients with MM have a preceding MGUS. At least 15% of patients with symptomatic MM produce no M 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 al 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 study 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.

ARTICLE INFORMATION

Author Affiliations: Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota.

Corresponding Author: Robert A. Kyle, MD, Division of Hematology, Department of Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (kyle.robert@mayo.edu).

Published Online: March 5, 2015. doi:10.1001/jamaoncol.2015.23.

Conflict of Interest Disclosures: None reported.

REFERENCES


Copyright 2015 American Medical Association. All rights reserved.