

Monoclonal gammopathy of undetermined significance: to screen or not to screen for multiple myeloma?

The UK Myeloma Forum and Nordic Myeloma Study Group recently published guidelines for the investigation of newly detected monoclonal protein (M-protein) and the management of monoclonal gammopathy of undetermined significance (MGUS) based on the review of evidence in the literature and consensus among a panel of medical experts and patient representatives (Bird *et al*, 2009). The panel acknowledged the deficiency of clinical trials to inform these guidelines and therefore, most recommendations were grade C, level IV.

For the management of MGUS, the option of no follow-up was not given equal emphasis by the panel. It was briefly mentioned as a consideration for the subgroup of patients with 'very short actuarial life expectancy (perhaps <5 years) and very low level of M-protein (say below 5 g/l).' The implication of the recommendations is that most patients outside of this subgroup should be monitored or screened for transformation to multiple myeloma (MM) and related malignancies every 3–4 months in the first year and every 6–12 months thereafter indefinitely. In fact, one could argue the opposite strategy of no additional follow-up outside of what is normally required and appropriate for the patient's age and existing co-morbid conditions other than MGUS for several reasons.

No study to date has shown any evidence of clinical benefit or significance of regular MGUS follow-up, i.e., survival advantage or less complication rate (hypercalcemia, pathological fractures, and dialysis-dependent chronic kidney disease), among those who developed malignant transformation compared to those with malignancies but did not have a preceding diagnosis of MGUS. On the contrary, a retrospective study from the Mayo Clinic suggested that among 1027 patients with newly diagnosed MM, there was no difference in overall survival between those with or without MGUS (Kyle *et al*, 2003).

Follow-up of MGUS is, by definition, screening for MM and related malignancies. Population screenings for MGUS and MM are not yet recommended in any cancer screening guidelines because of the overall low risk of transformation of MGUS (0.4% per year when competing causes of death taken into account) and the relative rarity of MM (1% of all cancers) (Rajkumar *et al*, 2005; Jemal *et al*, 2009). If we were to screen clinically diagnosed MGUS patients for MM, why should we not screen the entire population for subclinical MGUS, as we now know all MM are preceded by monoclonal gammopathy many years before MM diagnosis? After all, there is no evidence to suggest that MGUS incidentally detected

during evaluation of symptomatic patients is more likely to develop malignant transformation compared to MGUS intentionally detected by screening. In fact, the former group is likely to be older with co-morbidities and consequently has a higher chance of dying from other conditions. The median age at MGUS diagnosis is approximately 72 years with a median time to malignant transformation of about 11 years (Kyle *et al*, 2002). Therefore, most malignant transformation will occur when MGUS patients are in their eighth decade of life.

Currently, the cancers that we routinely screen for (breast, colorectal, prostate, endometrial, and cervical cancers) are potentially curable when diagnosed early, even though there may be debates regarding the actual impact on reduction in mortality at the population level. Such is not the case for MGUS or MM. There is also no intervention that can prevent or delay MGUS progression. In addition, it is expected that a substantial proportion of patients in whom malignant transformation occurs will either have smoldering MM or lymphoma in which observation is the standard of care. Fortunately, a long term follow-up study of MGUS showed that at 20 years, the death rate from MM and related malignancies was only 10% (72% from other conditions) (Kyle *et al*, 2002).

The best practice, in terms of frequency of provider evaluation and what appropriate tests to order, of monitoring patients with MGUS is unknown. The panel suggested an algorithm using the type of heavy chain and level of serum M-protein as a form of risk stratification and recommended routine quantification of M-protein and immunoglobulin levels among other tests. However, in the two most recent population-based studies (published after the guideline was written), the level of M-protein and serum free light chain ratio were not useful in predicting subsequent malignant transformation (Landgren *et al*, 2009; Weiss *et al*, 2009). In practice, MGUS patients in general may have a lower risk of dying from lymphoplasmacytic malignancies compared to asymptomatic stage IV low grade B-cell lymphoma patients. In the latter group, current guidelines from the National Comprehensive Cancer Network suggest that it is totally reasonable to follow the patients without any laboratory or imaging study. Tests may be ordered as clinically indicated (http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf).

Finally, the panel did not acknowledge the potential harms of indefinitely following MGUS. There may be psychological distress similar to that seen in screening the population at risk for other cancers or cancer patients in complete remission

being followed for relapse (van Dooren *et al*, 2004; Geurts *et al*, 2006). One also has to take note that unnecessary bone marrow biopsies, which may result as CRAB signs (hypercalcemia, renal failure, anemia, and bone pain or lesions), due to non-plasma cell disorders are expected to be common in the elderly population. The cost of health care utilization to the society can be tremendous due to the high prevalence of MGUS.

Until there is a treatment to eliminate MGUS as a pre-malignant condition or until we know MGUS is clinically significant, i.e., benefits of screening for MM and related malignancies outweigh the harms, health care providers should routinely provide informed discussion regarding both options of screening and no screening to patients newly diagnosed with MGUS.

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References

- Bird, J., Behrens, J., Westin, J., Turesson, I., Drayson, M., Beetham, R., D'Sa, S., Soutar, R., Waage, A., Gulbrandsen, N., Gregersen, H. & Low, E. & Haemato-oncology Task Force of the British Committee for Standards in Haematology, UK Myeloma Forum and Nordic Myeloma Study Group. (2009) UK myeloma forum (UKMF) and nordic myeloma study group (NMSG): guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS). *British Journal of Haematology*, **147**, 22–42.
- van Dooren, S., Rijnsburger, A.J., Seynaeve, C., Duivenvoorden, H.J., Essink-Bot, M.L., Tilanus-Linthorst, M.M., de Koning, H.J. & Tibben, A. (2004) Psychological distress in women at increased risk for breast cancer: the role of risk perception. *European Journal of Cancer (Oxford, England: 1990)*, **40**, 2056–2063.
- Geurts, T.W., Ackerstaff, A.H., Van Zandwijk, N., Hart, A.A., Hilgers, F.J. & Balm, A.J. (2006) The psychological impact of annual chest X-ray follow-up in head and neck cancer. *Acta Oto-Laryngologica*, **126**, 1315–1320.
- Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J. & Thun, M.J. (2009) Cancer statistics, 2009. *CA: a Cancer Journal for Clinicians*, **59**, 225–249.
- Kyle, R.A., Therneau, T.M., Rajkumar, S.V., Offord, J.R., Larson, D.R., Plevak, M.F. & Melton, 3rd, L.J. (2002) A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *The New England Journal of Medicine*, **346**, 564–569.
- Kyle, R.A., Gertz, M.A., Witzig, T.E., Lust, J.A., Lacy, M.Q., Dispenzieri, A., Fonseca, R., Rajkumar, S.V., Offord, J.R., Larson, D.R., Plevak, M.E., Therneau, T.M. & Greipp, P.R. (2003) Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proceedings*, **78**, 21–33.
- Landgren, O., Kyle, R.A., Pfeiffer, R.M., Katzmman, J.A., Caporaso, N.E., Hayes, R.B., Dispenzieri, A., Kumar, S., Clark, R.J., Baris, D., Hooever, R. & Rajkumar, S.V. (2009) Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood*, **113**, 5412–5427.
- Rajkumar, S.V., Kyle, R.A., Therneau, T.M., Melton, 3rd, L.J., Bradwell, A.R., Clark, R.J., Larson, D.R., Plevak, M.F., Dispenzieri, A. & Katzmman, J.A. (2005) Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood*, **106**, 812–817.
- Weiss, B.M., Abadie, J., Verma, P., Howard, R.S. & Kuehl, M. (2009) A monoclonal gammopathy precedes multiple myeloma in most patients. *Blood*, **113**, 5418–5422.

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Monoclonal gammopathy of undetermined significance: to screen or not to screen for multiple myeloma? – response

We welcome the opportunity to further explore the points made by Dr Go with respect to the recently published guidelines for the management of patients with newly diagnosed monoclonal gammopathy of undetermined significance (MGUS) (Bird *et al*, 2009). In his letter he states his belief that no specific follow up of individuals found to have MGUS is necessary other than that which would be appropriate for the patient's age and existing co-morbid conditions. We agree that no study to date has shown evidence of clinical benefit for

regular follow-up and have made this clear in our guideline. Despite this, MGUS is common and clinicians are often uncertain how to manage the condition. Due to the absence of evidence from large scale, prospective, randomized studies our group used clinical judgement in developing the advice given in the guidance.

A retrospective study from the Mayo Clinic suggested that, among 1027 patients with newly diagnosed myeloma, there was no difference in overall survival between those with or