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MGUS, multiple myeloma, and paratarg-7

Monoclonal gammopathy of undetermined significance (MGUS) is commonly associated with advancing age. Its significance in multiple myeloma hinges on the fact that patients who develop MGUS before the age of 60 years often go on to develop multiple myeloma. From a hereditary cancer perspective, the genotypic and phenotypic heterogeneity of multiple myeloma might be extremely important in ultimately determining its relationship with one or more hereditary cancer syndromes. In our search for a genetic basis for multiple myeloma, we need to pay attention to such things as age of cancer onset and other patient attributes that might differ among the different forms of the disease. There is a paucity of knowledge about hereditary factors in MGUS and multiple myeloma,^{1,2} which is unfortunate, considering the value of studying such patients and families whose lifetime risk of MGUS and multiple myeloma will significantly exceed that in the general population.³ But short of pedigree assessment, how do you identify individuals at increased risk for MGUS and multiple myeloma?

Grass and colleagues⁴ have shown that hyperphosphorylated paratarg-7 is the target of the monoclonal paraprotein present in a substantial proportion of patients with MGUS or multiple myeloma, and is present in multiple generations of families with MGUS or multiple myeloma. Proband in these families that had hyperphosphorylated paratarg-7 were found to be at an increased risk of developing MGUS and multiple myeloma (odds ratio [OR] 7.9; 95% CI 2.8–22.6; $p=0.0001$). Testing for a hyperphosphorylated carrier state will therefore be invaluable to identify those family members who are at an increased risk of developing MGUS and multiple myeloma, doing away with the need for pedigree assessment?

Grass and colleagues seem to assume an autosomal dominant inheritance. However, they also recognise that there remains a possibility that the hyperphosphorylation of paratarg-7 is an epiphenomenon resulting from common antigenic exposures in these kindreds. If the spouses of individuals affected with MGUS or multiple myeloma had been tested in these families, serving as internal controls, coupled with larger numbers of kindreds and, ideally, twin studies comparing monozygous with dizygous twin pairs, this research could have determined whether the hyperphosphorylation of paratarg-7 is a dominant trait versus an environmental phenomenon.

What are the implications of these findings? If chronic antigenic stimulation has a significant aetiological role in the pathogenesis of MGUS, and its progression to multiple myeloma, then logically the search for an explanation of the underlying autoimmunogenicity of paratarg-7 will provide an important target for preventive efforts in MGUS and multiple myeloma. Indeed, a causal relationship between neoplasms and antigenic stimulation was suggested almost 20 years ago.^{5,6}

Preuss and colleagues⁷ note that the frequency of paratarg-7, which is present in all human tissues, is believed to be directly, or indirectly, involved in the pathogenesis of the clonal proliferations that lead to MGUS and multiple myeloma. This accords with the view of Grass and colleagues that a significant proportion of MGUS and multiple myeloma might arise as a result of chronic antigenic stimulation. The IgG₃ subclass of the IgG paraproteins, and their restriction to paratarg-7, indicates that additional genetic factors might be necessary for the pathogenesis of multiple myeloma, but that paratarg-7 might have a role in autoimmunogenic activity in the respective patients.

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Clearly, this is a complex problem. We propose that epigenetic factors might stimulate the antigenic immunity that, in concert with a putatively dominantly inherited hyperphosphorylated protein, might then trigger molecular events that could involve low penetrant mutations and major germline multiple-myeloma-predisposing mutations; thereby accounting for the heterogeneous forms of multiple myeloma.¹

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Prophylactic cranial irradiation: going, going, gone



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With 5-year event-free survival reaching 80% or more in childhood acute lymphoblastic leukaemia (ALL), contemporary clinical trials must take into account not only the cure rate, but also the quality of life of the patients. In this issue of *The Lancet Oncology*, Veerman and colleagues¹ report the excellent results of their ALL-9 study, in which 5-year event-free survival was 81% and overall survival 86%. Notably, the results were achieved with treatment regimens associated with few long-term side-effects. Even for their high-risk patients, the doses of daunorubicin, cyclophosphamide, dexamethasone, and methotrexate were relatively low. The most radical feature of their clinical protocol is the omission of prophylactic cranial irradiation in all patients. Not surprisingly, they have reported only a few cases of osteonecrosis and only two cases of second malignancy among the 859 patients who were treated. The vast majority of their patients are expected to survive with an excellent quality of life.

Despite the omission of prophylactic cranial irradiation, only 2.6% of the patients in ALL-9 had isolated CNS relapses, three of which occurred among the 21 patients with overt CNS leukaemia (CNS3 status) at diagnosis. Similarly, in the two recent Total Therapy XIV and XV studies, in which cranial irradiation was also omitted for all patients, isolated CNS relapses occurred in none of 53 patients and in 11 of 498 patients (cumulative risk 2.7%; SE 0.8%), respectively.^{2,3} In Total Therapy XV, 5-year event-free survival was 85.6% (SE 2.9%), and all

11 patients with isolated CNS relapse have completed retrieval treatment and remain in second remission.³ Together, these results suggest that with effective chemotherapy, prophylactic cranial irradiation can be safely omitted from the treatment of childhood ALL. Hence, it will be important to determine definitive risk factors for the small subset of patients who continue to relapse in the CNS. While Veerman and colleagues did not do such analyses, the presence of any CNS involvement (CNS2, CNS3, or traumatic lumbar puncture with blast cells), T-cell ALL, and t(1;19)(TCF3-PBX1) were significant risk factors for CNS relapse in the Total Therapy trials.³ Ongoing clinical trials thus have further intensified early intrathecal treatment for patients with any of these features.

Even though the 5-year event-free survival of 84% reported by Veerman and colleagues for their non-high-risk cases was excellent, additional modifications of treatment might improve this outcome further. One approach would be to incorporate minimal residual disease measures into the criteria for risk-directed therapy. This strategy is supported by our results in 30 patients in Total Therapy XV who were reclassified by the presence of minimal residual leukaemia at the end of remission induction to receive intensified treatment. Each patient remained in remission at the time the study was published.³ Addition of re-induction treatment, as pioneered by the Berlin–Frankfurt–Münster group and subsequently confirmed by the

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