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NEOPLASIA

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Progression risk for MGUS and SMM

Philip Greipp MAYO CLINIC

Patients with monoclonal gammopathy of undetermined significance (MGUS) are at continuous risk of progression. Each year, 1% progress, usually to active multiple myeloma (MM).[1] Such patients must be monitored for life. Asymptomatic smoldering multiple myeloma (SMM) has an even greater risk of progression to MM. Recently reported strategies improve our ability to estimate the risk of MM in these patients.

In this issue of *Blood*, Pérez-Persona and colleagues show how an increasingly practical clinical laboratory technology, multiparameter flow cytometry, identifies groups of MGUS and SMM patients with differing risk. Eight percent of 407 MGUS patients and 51% of 93 SMM patients progressed to MM during 10 years of study. They identified phenotypically abnormal marrow plasma cells (PCs; $CD56^+/CD19^-$). Of MGUS patients, 127 had fewer than 95% of these aberrant PCs (aPCs), which lacked aneuploid DNA content. Their progression rate was 2% at 5 years (0.4% per year). SMM patients with fewer aPCs and normal levels of uninvolved immunoglobulin showed a risk of progression of 4% at 5 years (0.8% per year).

Does flow cytometric detection of aPCs improve risk estimation? Rajkumar et al showed, in a greater than 20 year follow-up, how the level and type of abnormal protein and the presence of serum monoclonal free light chain identify a group of patients with a low risk of progression.[1] Less than 1.5 g/dL M-protein of the IgG type, with no monoclonal serum-free light chain, conferred a progression risk of 0.25% per year compared with the 0.4% per year in the study by Perez-Persona et al. A direct comparison of datasets is impossible because serum-free light chain levels were not available to the investigators. However, they were able to show that flow cytometry detection of fewer aPCs plus lack of aneuploid DNA content lowered risk further than low levels of M-protein did. It follows that flow cytometry may add predictive value compared with standard clinical parameters.

For asymptomatic SMM patients, predictive analysis was performed in a recent 25-year follow-up. Annual progression rate was 10% for the first 5 years, 3% for the next 5 years, and 1% for the last 10 years.[2] Independent risk factors were percent marrow plasma cells and serum monoclonal protein level. Patients with less than 10% marrow PCs but more than 3 g/dL M-protein had the lowest risk of progression at 3% per year, similar to the 4% in the low-risk group in the Spanish study.

New molecular technologies may provide better prediction of progression in the future. A MGUS phenotype has been identified in good-prognosis MM patients by gene-expression profiling (GEP) of marrow DNA.[3] IL1-beta low expression identifies an MGUS-like subset of SMM.[4] While molecular methods hold promise, more development is required before they become practical. However, new flow cytometric technology already provides faster, more accurate digital analysis, with 6- and 8-color capability, allowing the identification of multiple CD markers to rapidly identify aPCs at the rate of 1 in 10 000, thus approaching the sensitivity of molecular minimal residual disease detection while at the same time allowing real-time and practical clinical use for phenoyping PCs.[5]

In the 35 years since the description of MGUS and the 27 years since the description of SMM, there has been increasing awareness of differing risk of progression. For current practice, patients with MGUS who have less than 1.5 g/dL monoclonal protein of the IgG type with a negative study for serum-free light chain have a risk of progression of 0.25% per year. They can be monitored at less frequent intervals of not more than once per year. Patients with SMM who have less than 10% PCs and more than 3 g/dL M-protein have a risk of development of MM of 3% per year. Because of new flow cytometry and molecular methods, we are on the threshold of more precisely identifying risk of progression in MGUS and SMM. This knowledge will be important for better understanding of the biology of MM, for better monitoring of patients at various levels of risk, and for the development of new strategies using biologic therapy aimed at delaying the progression of MGUS and SMM to active MM.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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