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S0120 G.E.M.S.: genomics encounters MGUS and SMM

Angela Dispenzieri

In this issue of Blood, Dhodapkar et al present the first US cooperative group trial in asymptomatic monoclonal gammopathies that prospectively examines state-of-the-art laboratory, genomic, and imaging as potential predictors for progression to active multiple myeloma.

This observational trial included 179 smoldering multiple myeloma (SMM) and 152 monoclonal gammopathy of unknown significance (MGUS) patients and illustrates both the feasibility and challenges of such a study: 331 eligible patients were accrued, but only 26% of MGUS patients and 49% of SMM had gene expression profiling (GEP) performed, and only 42% of MGUS and 51% of SMM patients had magnetic resonance imaging (MRI) completed.

All GEP-defined molecular subtypes seen in active multiple myeloma (MM) were present in MGUS and SMM, but only the proliferation subtype was predictive of progression. Neither hyperdiploidy nor any of the translocation subtypes was a risk factor for progression to active myeloma, which contrasts with the fluorescence in situ hybridization (FISH) findings that these factors are associated with higher rates of progression in SMM. In addition, in S0120, on univariate analysis, the GEP proliferative index and the polytypic plasma cell score were prognostic but lost significance once the powerful GEP-70 risk score was included. Since ~30% of genes in the GEP-70 score are from chromosome 1, this part of the S0120 data is concordant with the FISH data that demonstrated that chromosome 1q21 additions are a risk factor for SMM progression.

Based on Cox modeling, the authors generated 2 risk models for time to clinical progression requiring treatment. The first included only clinical variables: (1) serum M-spike ≥30 g/L; (2) bone marrow plasmacytosis ≥20%; and (3) age ≥65 years. The other more intriguing model included GEP and the following clinical variables: (1) GEP-70 ≥ 0.26; (2) involved serum immunoglobulin free light chain (FLC) >250 mg/L; and (3) serum M-spike ≥30 g/L. For both systems, patients were grouped according to whether they had no risk factors, 1 risk factor, or ≥2 risk factors. The clinical model without GEP yielded 3 groups with 2-year rates to MM requiring treatment of 3%, 14%, and 40%, respectively. The GEP containing model yielded 3 groups with 2-year rates to MM of 3%, 29%, and 71%, respectively. When the 39 patients with MGUS and available GEP data were excluded and the GEP based risk model was limited to the 79 SMM patients, the respective 2-year rates to MM requiring therapy increased marginally to 3%, 29%, and 71%, respectively.

Dhodopkar et al effectively used their dataset to test other published prognostic factors and systems, such as the one developed by Dispenzieri. Similar risk factors to what have been previously published were found in S0120, albeit with slightly different thresholds for some of the factors. The GEP-70/serum FLC/M-spike model was stronger than other published models, but the authors neglected to test the bone marrow plasma cell ≥60% threshold due to a paucity of patients satisfying that criterion. The authors indirectly tested the concept that the percent of aberrant vs polytypic plasma cells are a risk for progression, but find that the polytypic...
plasma cell score, albeit using a markedly different technique, was not a significant risk if the GEP-70 score was included in the model. Greater than 1 lesion on surveillance MRI was a very strong predictor of progression, despite the fact that it was a very rare event in the SWOG (formerly the Southwest Oncology Group) cohort, with only 6% tested patients having >1 focal lesion in their spines.

Should all patients with MGUS and SMM have GEP-70 scores generated? Before these data can be used for more than hypothesis generation, validation will be required. Time to progression for the S0120 MGUS population tracked well with the published literature; however, the rates for time to MM requiring therapy in the SMM group did not.

In the SWOG series, nearly 20% of SMM patients were deemed to have progressed at 1 year, and during the subsequent 3 years, the rate of progression was only approximately 3% per year. This contrasts markedly with the 10% per year rate affecting estimates of time to progression.1-7

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REFERENCES


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LYMPHOID NEOPLASIA

Comment on Jiang and Aguiar, page 86

Novel face of microRNA-155

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In this issue of Blood, Jiang and Aguiar1 present a novel mechanism in diffuse large B-cell lymphoma (DLBCL) cell lines by which microRNA (miR)-155 deregulate the crucial retinoblastoma protein (RB)/E2F cascade by repressing SMAD5. The resulting hyperphosphorylated RB is inactive and mediates unrestricted cell-cycle progression. Conversely, they demonstrate in mature B lymphocytes from miR-155 knockout (KO) mice elevated SMAD5 levels accompanied by a hypophosphorylated RB state and a more pronounced cell-cycle arrest. This might contribute to the reduced numbers of germinal center B cells and impaired T cell–dependent antibody response found in these mice.1

Despite recent advances in the understanding of the molecular pathogenesis of lymphomas, clinical parameters are still used to identify patients at risk receiving immunochemotherapy. A major step in deciphering molecular events in lymphomagenesis was the discovery of microRNAs (miRNA) and their causal involvement in multiple cancerous processes and tumor types. miRNA are small noncoding RNAs that posttranscriptionally regulate expression of target RNAs by reducing their stability. Mature miRNA are single-stranded molecules of 20-23 nucleotides in length that regulate gene expression in many physiological and pathological processes. In cancer, including lymphomas, miRNA dysregulation is a ubiquitous phenomenon; however, their exact functional role in lymphomagenesis has not been thoroughly investigated in many instances.2

Dysregulation of a single miR-155 in transgenic mice was the first report to prove that
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