Risk Stratification of Precursors to Multiple Myeloma in 2020

RANI CHUDASAMA, MD; PETER BARTH, MD

ABSTRACT

With advances in the treatment of plasma cell disorders, there have also been improvements in the risk stratification of these diseases. There are currently no screening recommendations for monoclonal gammopathy of unknown significance (MGUS); however, new studies are analyzing the role of screening for patients age 40–75 who are African American or have a family history of multiple myeloma (MM). Patients with smoldering multiple myeloma (SMM) have an increased risk of progression to MM when compared to MGUS. Data have shown that evaluation of bone marrow biopsy, full body MRI and free light chain ratios can identify high-risk SMM patients. Current investigation into early initiation of treatment for patients with SMM who do not meet criteria for MM showed improvement in time to progression. By continuing to evaluate clinical markers of disease burden, physicians can risk stratify patients to identify those at highest risk for progression to MM.

KEYWORDS: multiple myeloma, monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, risk stratification

INTRODUCTION

Over the past decade there have been significant advances in the management of plasma cell disorders. These developments are attributed primarily to novel myeloma-directed therapies, but also due to improved imaging techniques, analysis of the genetic evolution of plasma cell disorders (PCDs), and clinical trials exploring the treatment of pre-symptomatic stages of PCDs. Here we will explore recent advances in the risk stratification of monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and multiple myeloma. Of note, the evaluation of less common plasma cell disorders such as AL amyloidosis, Waldenström macroglobulinemia, POEMS syndrome, and monoclonal gammopathy of renal significance, is beyond the scope of this manuscript.

MGUS

MGUS is most often a diagnosis made in patients with a presentation concerning for multiple myeloma, but an alternative diagnosis is made to explain their presenting symptoms (e.g. renal failure due to dehydration, hypercalcemia due to hyperparathyroidism, iron deficiency anemia, etc.). The laboratory evaluation for plasma cell disorders includes a serum protein electrophoresis (SPEP), serum immunofixation (SIFE), serum free light chains (SFLC), quantitative immunoglobulin levels (IgG, IgA, IgM), and urine protein electrophoresis in patients with protein present on urinalysis. In order to be consistent with MGUS, the monoclonal protein must be <3 g/dL with <10% plasma cells present on a bone marrow biopsy. Both the quantity and quality of monoclonal protein are used to estimate risk of progression to myeloma in MGUS. The presence of 1. A non-IgG isotype, 2. Monoclonal protein > 1.5g/dl, or 3. An abnormal serum free light chain ratio have been found to increase risk of progression to myeloma. Patients with none, one, two, or all three risk factors have a 20-year risk of progression to multiple myeloma of 2%, 10%, 18%, and 27%, respectively.[1] In patients with low-risk MGUS (none of the aforementioned risk factors), bone marrow examination and skeletal survey can safely be deferred.[2,3] In all patients diagnosed with MGUS, regardless of risk category, the risk of progression to multiple myeloma remains linear, rather than logarithmic or exponential.

While MGUS is present in over 3% of patients aged 50 or older[4], there are currently no screening recommendations for the disease given the significant anxiety surrounding the diagnosis, the lack of curative therapy, and the low risk of progression to multiple myeloma. Investigation into who may benefit from screening for a monoclonal protein is ongoing with the current PROMISE study analyzing the role of screening in patients age 40–75 who are African-American or have a first-degree relative with multiple myeloma, MGUS, SMM, or Waldenström macroglobulinemia.

SMOLDERING MULTIPLE MYELOMA

Historically, those patients who do not have "CRAB" symptoms (hyper**c**alcemia >1 mg/dL above upper-limit of normal, **r**enal insufficiency with CrCl < 40 mL/min, anemia with hemoglobin value <10 g/dL, or one or more bone lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT) attributable to multiple myeloma, yet have ≥10% clonal bone marrow plasma cells on bone marrow examination or ≥3 g/dL of serum monoclonal protein are diagnosed with smoldering multiple

myeloma. This intermediate diagnosis reflects the increased risk of progression to symptomatic multiple myeloma compared to MGUS and thus can help guide clinicians on how to appropriately monitor these patients. Unlike the linear risk associated with MGUS over time, patients with smoldering multiple myeloma follow a logarithmic curve of progression to symptomatic multiple myeloma: 10% risk per year for the first five years following diagnosis, 3% risk per year for the following five years, and a subsequent 1% risk per year.[5]

Given the significant morbidity associated with symptoms of multiple myeloma, namely renal dysfunction, pain, and/or fracture associated with bone lesions, significant effort has been dedicated to identifying those patients with SMM who are very likely to progress. Long-term follow-up of SMM patients in a Mayo Clinic cohort revealed that the presence of >60% clonal plasma cells on bone marrow examination represents an ultra-high risk group of smoldering myeloma with a 95% risk of progression at two years.[6] Advances in MRI technology have allowed for a study of whole-body MRI in 149 patients with SMM found that two or more focal lesions on whole-body MRI indicated a 70% risk of progression to multiple myeloma at two years.[7] Subsequently, a retrospective study of free light chain levels in 586 patients with smoldering multiple myeloma discovered that an involved-to-uninvolved free light chain ratio of 100:1 or greater predicted a 72% risk of progression to multiple myeloma within two years.[8] These three studies led to the incorporation of three new diagnostic criteria for multiple myeloma by the International Myeloma Working group (IMWG): 1. Bone marrow clonal plasma cells >60%; 2. Involved-to-uninvolved free light chain ratio >100:1 (also requiring the involved free light chain absolute level >100 mg/L); and 3. >1 focal lesion on MRI studies.

More recently, focus has shifted toward identifying SMM patients who do not meet the aforementioned criteria for multiple myeloma who would benefit from early initiation of therapy. The Spanish PETHEMA group published a phase 3, open-label, randomized trial of lenalidomide and dexamethasone versus observation in high-risk SMM (defined as SMM plus >95% phenotypically aberrant plasma cells in the bone marrow plasma cell compartment with reduction of at least 25% below the lower-limit of normal in one of the two uninvolved immunoglobulins) in 2016.[9] Patients in the intervention arm had a significantly longer time to progression (HR 0.24, 95%CI 0.14–0.41) as well as a significant improvement in overall survival (0.43, 95%CI 0.21–0.92). Unfortunately, the risk stratification method using multi-parameter flow cytometry is of limited availability in many practices and is not routinely performed. Early results from an ongoing Eastern Cooperative Oncology Group Study (E3A06) have confirmed the expected improvement in time to progression, without overall survival data available. This trial uses routinely available markers of high-risk SMM of > 20% clonal bone marrow plasma cells, >2 g/dL monoclonal protein or involved-to-uninvolved free light chain ratio of >20:1.

CONCLUSION

As basic science advances our understanding of the evolution from the asymptomatic precursor disease of MGUS to symptomatic multiple myeloma, clinical research is investigating the benefits of treating patients earlier in their disease course with the hope of preventing morbidity. The convergence of these two processes is the development of a safe and effective cure for plasma cell disorders at diagnosis. Until that time, the use of clinical markers of disease burden can help physicians risk stratify patients in order to counsel on appropriate testing, referral, follow-up, and treatment.

References

1. S. Rajkumar, R. Kyle, T. Therneau, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood*. 2005;106:812-817. doi: 10.1182/blood-2005-03-1038
2. R. Go and V. Rajkumar. How I manage monoclonal gammopathy of undetermined significance. *Blood*. 2018;131:163-173. doi: 10.1182/blood-2017-09-807560
3. N. van de Donk, T. Mutis, P. Poddighe, et al. Diagnosis, Risk Stratification and Management of Monoclonal Gammopathy of Undetermined Significance and Smoldering Multiple Myeloma. *Int J Lab Hematol*. 2016;38:110-122. doi: 10.1111/ijlh.12504
4. R. Kyle, T. Therneau, S. Rajkumar, et al. Prevalence of Monoclonal Gammopathy of Undetermined Significance. *N Engl J Med*. 2006;354:1362-1369. doi: 10.1056/NEJMoa054494
5. R. Kyle, E. Remstein, T. Therneau, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med*. 2007;356:2582-2590. doi: 10.1056/NEJMoa070389
6. S. Rajkumar, D. Larson and R. Kyle. Diagnosis of Smoldering Multiple Myeloma. *N Engl J Med*. 2011;365:474-475. doi: 10.1056/NEJMc1106428
7. J. Hillengass, K. Fechtner, M. Weber, et al. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. *J Clin Oncol*. 2010;28:1606-1610. doi: 10.1200/JCO.2009.25.5356
8. J. Larsen, S. Kumar, A. Dispenzieri, et al. Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma. *Leukemia*. 2013;27:941-946. doi: 10.1038/leu.2012.296
9. M. Mateos, M. Hernández, P. Giraldo, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2016;17:1127-1136. doi: 10.1016/S1470-2045(16)30124-3

Authors

Rani Chudasama, MD; Alpert Medical School of Brown University, Division of Hematology Oncology, Rhode Island Hospital/The Miriam Hospital, Providence, RI.

Peter Barth, MD; Assistant Professor of Medicine, Alpert Medical School of Brown University, Division of Hematology-Oncology, Rhode Island Hospital/The Miriam Hospital, Providence, RI.

Correspondence

Peter Barth, MD
Lifespan Cancer Institute
The Miriam Hospital
Fain Building, 2nd Floor
164 Summit Ave., Providence, RI, 02906
401-793-7151, Fax 401-793-2855
peter_barth@brown.edu