

ADVANCES IN LLM

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When to Initiate Treatment in Smoldering Multiple Myeloma



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H&O How is smoldering multiple myeloma defined?

MM Smoldering multiple myeloma is a plasma cell disorder defined by the presence of a serum monoclonal component of at least 30 g/L and/or between 10% and 60% plasma cells in the bone marrow. It is an asymptomatic disease.

Approximately 2% of patients with smoldering multiple myeloma will develop myeloma-defining events, which include the presence of hypercalcemia, renal failure, anemia, or bone disease. These criteria, known as CRAB, were expanded in 2015 by the International Myeloma Working Group to include elevated immunoglobulin-free light chains (in which the involved light chains are 100 times more numerous than the uninvolved ones), plasma cell bone marrow infiltration exceeding 60%, and 2 or more focal lesions identified during magnetic resonance imaging (MRI). These biomarkers should be considered myeloma-defining events.

H&O How is smoldering multiple myeloma diagnosed?

MM The first sign of smoldering multiple myeloma is elevation of the serum total proteins. This finding should lead to serum protein electrophoresis to detect the presence of a monoclonal component. When the monoclonal component is higher than 3 g/dL, we perform a bone marrow aspirate, with or without a biopsy. If the plasma cells within the bone marrow are between 10% and 60%, smoldering multiple myeloma should be suspected. However, a hemogram must be performed to exclude anemia,

and biochemistry tests are needed to evaluate renal function, calcium levels, and liver function. Physicians should also check for the presence of bone lytic lesions, which indicate active multiple myeloma instead of smoldering multiple myeloma. Although bone lesions can be evaluated with a conventional X-ray, this method is less sensitive than low-dose computed tomography. In fact, low-dose computed tomography can be considered the new standard of care for the evaluation of lytic lesions.

The presence of high-risk cytogenetic abnormalities in smoldering multiple myeloma predict a higher risk of progression to active multiple myeloma.

All patients with smoldering multiple myeloma should undergo testing of the serum free light chain ratio, as well as MRI. Active multiple myeloma is diagnosed if the serum free light chain ratio is higher than 100, or if 2 or more focal lesions are identified during an MRI.

After the initial diagnosis of smoldering multiple myeloma, a hemogram, biochemistry tests, and protein studies should be repeated in approximately 2 or 3 months to confirm the stabilization of the monoclonal

component, as well as the absence of anemia, renal impairment, and hypercalcemia. At this point, the diagnosis of smoldering multiple myeloma can be confirmed.

H&O How is smoldering multiple myeloma distinguished from MGUS and other plasma disorders?

MM Monoclonal gammopathy of undetermined significance (MGUS) is also an asymptomatic plasma cell dyscrasia. In this entity, the level of serum monoclonal protein must be less than 3 g/dL, and the plasma cell bone marrow infiltration must be less than 10%. When evaluating plasma cell dyscrasias, the differential diagnosis should include MGUS, smoldering multiple myeloma, and active multiple myeloma. The monoclonal component as well as the plasma cell bone marrow infiltration can be used to distinguish MGUS from smoldering multiple myeloma. Both of these asymptomatic entities can be distinguished from active multiple myeloma, which will always manifest with myeloma-defining events.

H&O Are there any recent insights into the genetics of smoldering multiple myeloma?

MM The presence of high-risk cytogenetic abnormalities in smoldering multiple myeloma predicts a higher risk for progression to active multiple myeloma. The primary abnormalities inducing the transformation of a normal plasma cell to a pathologic plasma cell are already present in smoldering multiple myeloma and MGUS. These genetic events include hyperdiploidy and immunoglobulin (Ig) H translocations. The transition from smoldering multiple myeloma to active multiple myeloma is associated with additional genetic events, which likely involve mutations in the *MYC* and *KRAS* genes, the chromosome 13 deletion, and abnormalities in the 17p chromosome.

H&O What models are used to determine the risk for progression to active multiple myeloma?

MM Two risk models have been validated in clinical trials. A risk model from the Mayo Clinic considers the size of the monoclonal component together with the plasma cell bone marrow infiltration. In patients with a monoclonal protein level exceeding 3 g/dL and more than 10% plasma cell bone marrow infiltration, the median time to progression to active myeloma is approximately 2 years. In an intermediate group of asymptomatic patients who have more than 10% of plasma cells in the bone marrow and a monoclonal component of less than 3 g/dL, the median time to progression is approximately 8 years.

When the monoclonal component exceeds 3 g/dL, but the plasma cell bone marrow infiltration is less than 10%, the median time to progression is approximately 20 years. This risk model is used widely around the world because the size of the monoclonal component and the level of plasma cell bone marrow infiltration are known for all patients with smoldering multiple myeloma.

A risk model proposed by the Programa para el Tratamiento de Hemopatías Malignas (PETHEMA) Spanish Myeloma Group incorporates the percentage of clonal plasma cells within the plasma cell bone marrow compartment. If a smoldering multiple myeloma produces IgG, then levels of the other immunoglobulins that are not involved—IgA and IgM—are decreased. This scenario indicates high risk, with a median time to progression of approximately 2 years.

There are several other risk models in use, which are based on cytogenetic abnormalities, positron emission tomography, computed tomography, or gene expression profiling. Evolution of the monoclonal component over time forms the basis of a risk model from Barcelona, which was validated by the Mayo Clinic. High-risk factors include a monoclonal component that increases over time, a hemoglobin level that decreases by at least 0.5 g/dL within the first year, and a plasma cell bone marrow infiltration that is higher than 20%. In these patients, the risk for progression to myeloma is extremely high, at almost 80% at 2 years.

With these very different risk models, it can be difficult for physicians to know how to proceed. To simplify the situation, the International Myeloma Foundation, the Mayo Clinic group, and the PETHEMA Spanish Myeloma Group are planning to evaluate approximately 5000 patients with smoldering multiple myeloma worldwide to establish a simple score that will predict the risk for progression to active multiple myeloma. This score should be available in 2018.

H&O How do you counsel patients about their risk for progression to active multiple myeloma?

MM In most cases, we can explain to the patient that the probability of progression to active multiple myeloma is very low, at approximately 1% per year. These patients require follow-up visits just once per year. In patients at intermediate risk for progression, the risk is approximately 3% per year. In these cases, patients require visits twice per year, especially at the beginning. If their monoclonal component remains stable, we might change to one follow-up visit per year.

The situation becomes more complicated with patients who are at high risk for progression, for example, 50% after 2 years. We must inform them that

the median time to progression to myeloma is approximately 2 years. The best option is to enroll these patients in a clinical trial. Currently, no drugs are approved for the treatment of smoldering multiple myeloma.

H&O What factors indicate that initiation of treatment should be considered?

MM Treatment should be initiated when the serum-free light chain ratio is higher than 100, the bone marrow consists of more than 60% plasma cells, or MRI identifies 2 or more focal lesions. These patients are still asymptomatic, but the presence of these characteristics indicates that progression to active multiple myeloma is imminent.

H&O What are the treatment options?

MM In 2013, the PETHEMA Spanish Myeloma Group conducted a randomized phase 3 trial focused on asymptomatic myeloma patients at high risk for progression to myeloma. The trial demonstrated that early treatment with lenalidomide (Revlimid, Celgene) and dexamethasone delayed time to progression to active disease, and provided a significant improvement in overall survival. These results are extremely relevant, pending confirmation by other ongoing trials.

Currently, more than 50 clinical trials are being conducted in patients with high-risk smoldering multiple myeloma. There are 2 treatment approaches. One attempts to delay progression to active disease and consists of regimens that combine lenalidomide and dexamethasone with other therapies, such as checkpoint inhibitors, monoclonal antibodies, elotuzumab (Empliciti, Bristol-Myers Squibb), and ixazomib (Ninlaro, Takeda). Elotuzumab is a monoclonal antibody targeting SLAMF7, which is present on the surface of plasma cells and natural killer cells. Ixazomib is a second-generation proteasome inhibitor.

The other treatment approach aims to cure asymptomatic multiple myeloma. The Spanish Myeloma Group recently completed recruitment of a trial in which 90 patients with high-risk smoldering multiple myeloma will receive induction with carfilzomib, lenalidomide, and dexamethasone; transplant; consolidation with the same induction regimen; and maintenance with lenalidomide. A similar approach, which will incorporate the addition of a monoclonal antibody, will be evaluated in a study in the United States currently under development by Drs Shaji Kumar and Brian Durie.

H&O Are there any unmet needs in smoldering multiple myeloma?

MM We need a homogenous risk model that can be used worldwide to define the risk for progression to active multiple myeloma. If different trials use different risk models, then they might identify different patient populations. As I mentioned, we hope to develop a simple score.

We also need to know more about the transition from MGUS, to smoldering multiple myeloma, and to active multiple myeloma. Which genetic events cause progression from one entity to another? Studies should explore the plasma cells as well as the bone marrow microenvironment. Clinical trials would be the optimal approach to the investigation of these issues.

Disclosure

Dr Mateos has received honoraria for lectures and participation in advisory boards from Janssen, Celgene, Amgen, and Takeda.

Suggested Readings

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