

Smouldering myeloma: What Lauren Laverne's diagnosis means for patients

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Lauren Laverne's recent announcement of a smouldering myeloma diagnosis has brought a rare spotlight to a condition many clinicians still consider a diagnostic grey area. This precursor to active multiple myeloma presents a unique challenge: identifying patients at high risk of progression while avoiding overtreatment in those who may never develop symptomatic disease. The distinction between smouldering myeloma and active myeloma hinges on the absence of end-organ damage, a key factor in determining management.

KEY TAKEAWAYS

- ° The Pivot: Smouldering myeloma is a distinct clinical entity, not merely an early stage of active multiple myeloma, requiring careful risk stratification.
- ° The Data: While progression to active myeloma is not universal, a significant proportion of patients will develop symptomatic disease, necessitating vigilant monitoring.
- ° The Action: Clinicians must distinguish smouldering myeloma from active disease based on CRAB criteria and risk-stratify patients to guide monitoring frequency and potential intervention.

Smouldering multiple myeloma (SMM), also known as asymptomatic myeloma, is defined by the presence of monoclonal plasma cells in the bone marrow (typically 10-60%) or a monoclonal protein in the serum (M-protein $\geq$ 3 g/dL) or urine, but importantly, without any myeloma-defining events (MDEs). These MDEs, often referred to by the acronym CRAB, include hypercalcaemia, renal insufficiency, anaemia, and bone lesions. The absence of these symptoms is what differentiates SMM from active, symptomatic multiple myeloma. This distinction is paramount for patient management, as active myeloma requires immediate treatment, while SMM typically involves watchful waiting.

The underlying mechanism of SMM involves the clonal proliferation of plasma cells in the bone marrow. These abnormal cells produce a monoclonal immunoglobulin, which can be detected in blood or urine. While these cells are malignant, they do not yet cause the systemic damage characteristic of active myeloma. The progression from SMM to active myeloma is a continuous spectrum, driven by an accumulation of genetic abnormalities and changes in the bone marrow microenvironment. Understanding this progression is central to identifying patients who might benefit from early intervention versus those who can be safely monitored.

Defining the Risk of Progression

Not all patients with smouldering myeloma will progress to active disease. The annual risk of progression is highest in the first five years following diagnosis, then gradually declines. This variability makes risk stratification essential. Clinicians use several factors to assess a patient's individual risk, including the size and type of the M-protein, the

percentage of plasma cells in the bone marrow, and the presence of certain genetic abnormalities. Patients with higher levels of M-protein or a greater burden of plasma cells generally face a higher risk of progression.

The International Myeloma Working Group (IMWG) has established criteria to help stratify risk. High-risk SMM is typically defined by specific biomarkers that indicate a higher likelihood of progression to active myeloma within two years. These biomarkers include a bone marrow plasma cell percentage of 60% or more, a serum free light chain ratio of 100 or more, or more than one focal lesion on MRI. Patients meeting these criteria are considered to have a very high risk of progression, approaching that of active myeloma, and may be candidates for clinical trials exploring early intervention strategies. For a deeper dive into novel therapies in this space, our coverage on CELMoDs in relapsed/refractory multiple myeloma offers further context.

Monitoring and Management Strategies

The standard of care for most patients with smouldering myeloma remains active surveillance, often termed 'watch and wait'. This involves regular monitoring of blood and urine parameters, as well as periodic bone marrow biopsies and imaging studies. The frequency of monitoring depends on the patient's risk stratification. Patients with low-risk SMM might be monitored every 6-12 months, while those with high-risk SMM may require more frequent assessments, perhaps every 3-6 months. The goal is to detect the earliest signs of progression to active myeloma, allowing for timely initiation of treatment.

The decision to initiate treatment is typically reserved for when a patient develops symptomatic active myeloma, as defined by the CRAB criteria or other myeloma-defining events. This approach aims to avoid the toxicities and potential side effects of anti-myeloma therapies in patients who may never progress or who may progress very slowly. But, the psychological burden of living with a 'watch and wait' diagnosis can be substantial for patients. The uncertainty and the constant threat of progression can significantly impact quality of life, a factor that clinicians must acknowledge and address through supportive care and clear communication.

Imaging plays an essential role in monitoring SMM. Whole-body low-dose computed tomography (WBLDCT) and magnetic resonance imaging (MRI) are used to detect bone lesions, which are a key indicator of progression to active myeloma. Positron emission tomography-computed tomography (PET-CT) can also be used to identify metabolically active lesions. These imaging modalities help to identify patients who might have occult bone disease, which would reclassify their condition as active myeloma requiring treatment. The efficacy of bispecific antibodies in multiple myeloma with renal impairment highlights the importance of early detection and tailored treatment.

The Role of Early Intervention Trials

For high-risk smouldering myeloma, the clinical trial pipeline is slowly shifting. While watchful waiting remains the standard, clinical trials are investigating whether early intervention with anti-myeloma therapies can delay or prevent progression to active disease. These trials often use drugs approved for active myeloma, such as immunomodulatory drugs or proteasome inhibitors, in an earlier setting. The rationale is that by treating the underlying clonal plasma cell population before it causes irreversible organ damage, patients might experience better long-term outcomes. But, the challenge lies in balancing the potential benefits of delaying progression against the risks of treatment-related toxicities in asymptomatic individuals.

These early intervention studies are complex. They require careful patient selection, robust endpoints, and long follow-up

periods to demonstrate a meaningful clinical benefit. The primary endpoint in many of these trials is progression-free survival (PFS) or time to progression to active myeloma. While some studies have shown a delay in progression with early treatment, the impact on overall survival (OS) is still being evaluated. The field is cautious, as overtreating patients with a condition that may never become symptomatic is a significant concern. The use of isatuximab quadruplets in active myeloma shows the intensity of treatment required once the disease progresses.

The open-label design of many early intervention trials is an obvious caveat. The psychological impact of knowing one is receiving active treatment versus placebo can influence patient-reported outcomes. These trials are not powered to detect differences in rare subgroups, and that gap matters for individualised patient care. The long-term safety profile of these therapies in an asymptomatic population is also a critical consideration. Clinicians must weigh the known risks of treatment against the uncertain benefit of delaying progression, particularly when the natural history of SMM is so variable. For a comprehensive overview of current management, the Oxford Handbook of Oncology provides a concise reference.

Future Directions and Unanswered Questions

The future of smouldering myeloma management will likely involve more precise risk stratification tools, potentially incorporating advanced genomic profiling and minimal residual disease (MRD) assessment. Identifying patients with ultra-high-risk SMM who are virtually certain to progress could justify earlier, more aggressive interventions. Conversely, identifying those with truly indolent disease could allow for less intensive monitoring, reducing patient anxiety and healthcare burden. The goal is to move towards a more personalised approach, where treatment decisions are tailored to the individual patient's risk profile and preferences.

The field continues to grapple with several unanswered questions. What is the optimal duration of early intervention therapy? Are there specific subgroups of SMM patients who derive the most benefit from early treatment? How do we best incorporate patient preferences and quality of life considerations into treatment decisions for an asymptomatic condition? These questions highlight the complexity of SMM and the ongoing need for rigorous research. The ongoing evolution of BCMA bispecifics in community myeloma care highlights the rapid pace of therapeutic development in this area.

CLINICAL IMPLICATIONS

Lauren Laverne's public diagnosis of smouldering myeloma is a double-edged sword. It raises awareness, which is good, but it also risks creating undue anxiety among patients who may have a very low risk of progression. Clinicians must be prepared to explain the nuances of SMM, emphasising that it is not active cancer and that watchful waiting is often the most appropriate initial strategy.

The temptation to intervene early, especially with effective new agents, is strong. But, we must resist the urge to treat a number on a lab report if there is no clear clinical benefit to the patient. The long-term toxicities of anti-myeloma therapies are not trivial, and exposing asymptomatic individuals to these risks without a definitive survival advantage is questionable practice. The focus should remain on identifying true high-risk patients who are on the cusp of symptomatic disease.

For patients, the psychological burden of a smouldering diagnosis cannot be overstated. GPs and specialists alike need to provide clear, empathetic communication, explaining the difference between smouldering and

active disease and outlining the monitoring plan. This is where the art of medicine meets the science, ensuring patients feel supported and informed, not just observed.

The ongoing research into early intervention for high-risk SMM is vital. If future trials demonstrate a clear, long-term survival benefit without excessive toxicity, the paradigm may shift. Until then, precision in diagnosis and careful, individualised monitoring remain the cornerstones of managing this complex precursor condition.

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