MultipleMyelomaHub

General MM

# IMW 2019 | Smoldering Myeloma

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During the XVII International Myeloma Workshop (IMW) in Boston, US, a session of debates on hot topics in multiple myeloma (MM) was held. One of the topics debated was whether we should treat smoldering multiple myeloma (SMM). SMM was previously one of the MM Hub's educational themes, so we are pleased to provide updated coverage from the debate between Prof. Irene Ghobrial, who argued we should treat SMM, and Dr Angela Dispenzieri who argued we should not (**Table 1**).[1]

**Table 1.** Summary of debate entitled: Should we treat smoldering MM (SMM)?[1]

| **Irene Ghobrial – YES, we should treat SMM** | **Angela Dispenzieri – NO, we should not treat SMM** |
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| • Currently, there is no SMM screening process<br>• Patients with SMM are often observed until progression to active disease before treatment is given<br>• In other malignancies, clinicians do not wait until patients have end-organ damage or bone fractures to treat | • At 10 years, around 50% of patients in low- and intermediate-risk SMM groups have not progressed to active MM<br>• Is it ethical to over-treat patients who will never progress to active disease? |
| • The 2014 revised International Myeloma Working Group (IMWG) guidelines recommended ultra-high risk SMM treated as myeloma;<br>  • Existing precedent to reclassify certain patients and change the treatment approach.[2] | • New Mayo Clinic 20:20:2 model of risk progression*, means patients roughly fit within a 1:1:1 ratio of low *vs* standard *vs* high risk[3]<br>• Low-risk patients have 5% risk of progression per year[3]<br>• High-risk patients should potentially be reclassified as having active myeloma<br>• Goal of treatment in 2019, compared to 2014, could be to treat patients who have an 80% risk of progression at five-years<br>• Fluorescence *in situ* hybridization (FISH) classification could indicate those at high-risk of progression |

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| • Phase III randomized clinical trials in SMM have shown benefit in treating asymptomatic high-risk SMM with lenalidomide compared to observation alone (example: E3A06 trial) | • Patients chosen for phase III trials of early intervention in SMM were a high-risk population<br>• Many would now be reclassified as having active myeloma according to the new SMM risk criteria, such as the Mayo 20:20:2 model[3] |
| Key requirements to make early intervention in SMM possible and safe:<br>1. Only treat patients who are highly likely to progress: accurate risk stratification and consensus definitions are required<br>2. Treat with therapies that eradicate the early (progenitor) clones of MM: better, targeted therapies are required to avoid clonal selection<br>3. Re-normalize the microenvironment<br>4. Use therapies without additional toxicity, and that do not require a long duration of treatment: define optimal duration of therapy | • Interaction between myeloma cells and the immune cells in the microenvironment is not well understood<br>• We cannot tell the difference between SMM and MM by looking at genetic events<br>• There is a need to accurately discern between monoclonal gammopathy of undetermined significance (MGUS), SMM and MM (using FISH, genome expression profiling [GEP] or whole genome sequencing [WGS]), in order to develop agents to intercept the right processes<br>• Advances in the genomic definition of SMM and MM are crucial before we routinely treat patients with SMM |
| • Precision medicine in the future may allow treatment of specific patients at high risk of progression with targeted, highly active, agents | • If we seek to prevent morbidity:<br>  • Indefinite therapy may induce morbidity itself following 10–20 years of usage<br>  • Risk of overtreatment of low-progression risk population |
| Both debaters reached consensus that SMM should ultimately be treated, but only in those at high-risk of progression to prevent over treatment. In order to do this, both acknowledged that we need to be able to better identify patients at risk of progression and treat them with appropriate targeted therapy. Therefore, we should treat not treat SMM… yet! | |

*Bone marrow plasma cells [BPMC] >20%, M-protein >2g/dL and free light chain ratio [FLCr] >20[3]

After the debate concluded, the MM Hub conducted a poll on Twitter which found 69% of voters agreed with Dr Dispenzieri that we should not treat SMM.

The MM Hub has previously covered this controversial topic as a detailed write-up of a similar debate held at the 5th World Congress on Controversies in Multiple Myeloma (COMy), and as an expert discussion between Prof. Maria-Victoria Mateos and Dr Francesca Gay at the American Society of Clinical Oncology (ASCO) meeting (video below).

Click the links here to read more about risk stratification in SMM, and the genomics of SMM.

**References**

1. Great debates in myeloma. XVII International Myeloma Workshop (IMW). 2019 Sep 15. Oral debates and presentations.

2. Rajkumar V. *et al*., International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Onc. 2014 Oct 26. DOI: 10.1016/S1470-2045(14)70442-5.

3. Lakshman A. *et al.,* Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. Blood Canc J. 2018 Jun 12. DOI: 10.1038/s41408-018-0077-4