Should high-risk smouldering multiple myeloma be treated?

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Opening opinion: Yes

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Smouldering multiple myeloma is the asymptomatic intermediate stage between the premalignant stage of clonal plasma cell proliferation known as monoclonal gammopathy of uncertain significance (MGUS) and multiple myeloma. Primary genetic events play a major role in the development of MGUS, and progression to multiple myeloma occurs as a result of further genetic changes to the plasma cell clone. Smouldering multiple myeloma has a variable clinical course and cannot be distinguished genomically or morphologically from multiple myeloma; with half of the patients progressing to multiple myeloma in the first 5 years and a third remaining free of progression at 10 years. No molecular marker exists that will reliably differentiate patients with MGUS who do not progress from those who will progress to myeloma and therefore merit earlier treatment. Current attempts to stratify patients with smouldering multiple myeloma by risk of progression have relied heavily on tumour burden rather than the biology of the disease. Lakshman and colleagues have proposed a new risk stratification model, in which high-risk features included bone marrow plasma cell percentage of more than 20%, free light chain ratio of more than 20, and high-risk cytogenetics (del 17p, t[4;14], or hyperdiploidy). Median time to progression for patients with high risk (two features) was 14·5 months (95% CI 10·7–25·4), for those with intermediate risk (one feature) was 63·0 months (29·8–not reached), and for low-risk patients was not reached (33·3 months–not reached). In a retrospective cohort study, Bolli and colleagues analysed whole genomes of paired samples of 11 patients with smouldering multiple myeloma who progressed to multiple myeloma. They observed two main patterns of progression. The first was a neutral tumour evolution, which occurred in 20% of cases, wherein the genomic features of an overt multiple myeloma were already present at the smouldering stage and the same subclonal architecture was retained during progression. For these patients, time to progression seemed to be short and might reflect the time needed to accumulate the disease burden for symptomatic multiple myeloma to develop. The second is a Darwinian model, which occurred in 80% of cases, wherein the subclonal composition changed from smouldering to overt multiple myeloma due to additional mutations acquired over time that offer a proliferative advantage to one of the subclones. For these patients, time to progression seems to be variable. They hypothesised that the first group may be treated as multiple myeloma while the second group may be candidates for preventive therapeutic interventions. Goals of current and future trials in smouldering multiple myeloma include developing treatment regimens that can eradicate all clones and prevent clonal evolution by aiming for a high complete response with no minimal residual diasease, or strategies that aim to delay clonal evolution by modifying the microenvironment and achieve durable disease control. Two studies of intensive therapy aiming for the former are the GEM-CESAR (NCT02415413) and ASCENT (NCT03289299) trials. In GEM-CESAR, of the 90 patients with high-risk smouldering multiple myeloma enrolled, 84 (93%) remain progression free at 30 months and 51 (61%) of 83 patients who completed induction, transplantation, and consolidation achieved minimal residual disease negativity. If aiming to delay clonal evolution, modification of the tumour microenvironment can be done with immunomodulatory drugs. Several trials are ongoing. The ECOG-E3A06 trial reported improved progression-free survival with lenalidomide compared with placebo. With elotuzumab, lenalidomide, and dexamethasone

(NCT02279394), presented at the American Society of Hematology Annual Meeting 2018, 41 (84%) of 49 patients had an overall response. In patients treated with ixazomib, lenalidomide, and dexamethasone (NCT02916771), 23 (88%) of 26 had an overall response. The CENTAURUS trial (NCT02316106) is assessing the effect of three different dose schedules of daratumumab, and 2-year progression-free survival is 90% in the group of patients receiving the longer dosing schedule. In conclusion, we contend that, in smouldering multiple myeloma, it is important to biologically distinguish the cases with low proliferative potential from those with high proliferative potential, and would recommend treating the aggressive counterpart early to prevent or delay clonal evolution.

Counter opinion: No

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The definition of smouldering multiple myeloma includes patients with 10% of monoclonal plasma cells in the bone marrow, or a monoclonal component of 3gr/dl in serum or 0·5 gr/dl in urine without evidence of end-organ damage related to multiple myeloma. Despite this precise definition, smouldering multiple myeloma is not a unique disease, but rather a heterogeneous spectrum of clinically, biologically and genetically different entities, some with an indolent behaviour, closer to MGUS, and others representing a premalignant condition with a high risk of progression to symptomatic multiple myeloma. Traditionally, the presence of hypercalcemia, renal failure, anaemia, or bone lesions was necessary to define active multiple myeloma requiring treatment. With the aim of preventing multiple myeloma-related comorbidities, the International Myeloma Working Group (IMWG) broadened this definition including bone marrow plasmacytosis ≥60%, >1 focal lesion on MRI, or >100 FLC ratio as biomarkers of active disease, since any of these three parameters are associated with roughly a 80% risk of progression to overt multiple myeloma at 2 years.

In an era of highly effective anti-multiple myeloma drugs, early intervention in patients with high-risk smouldering multiple myeloma has the potential not just for a delayed progression to overt multiple myeloma, but for a definitive cure. Whether patients with smouldering multiple myeloma should be recommended early therapy has therefore become a burning question. Several single-arm studies of early intervention with novel agents have been conducted in patients with smouldering multiple myeloma, but only two randomised clinical trials have compared active treatment versus observation in this population. In the phase 3, QUIREDEX study, early treatment of patients with high-risk smouldering multiple myeloma with lenalidomide and dexamethasone improved time to progression and overall survival compared with observation. More recently, in the ECOG-E3A06 study, single-agent lenalidomide significantly improved the progression from high-risk smouldering multiple myeloma to symptomatic multiple myeloma in comparison with observation, but overall survival has not been reported yet. Given these positive results, it is reasonable to ask whether early intervention should become standard practice. We think that considering all the available evidence, the answer is still no, as several important questions remain unanswered.

The first issue is the current definition of high-risk smouldering multiple myeloma. Several parameters (mostly based on serum M protein and plasma cell infiltration of the bone marrow) and risk scores have been used in clinical trials without consistency. Recently, a new stratification model has been proposed by the IMWG. With this model, while 50% of patients had disease progression at 2 years, approximately one third did not at 5 years; as such, treating all high-risk patients may lead to overtreatment in a significant number of patients.

A second issue is whether recommendation for early intervention should be solely based on the results from the two randomised studies done so far, both of which had important limitations. QUIREDEX was done before the revision of the IMWG diagnostic criteria, thus possibly including patients with multiple myeloma rather than smouldering multiple myeloma. This possibility was highlighted by the GEM-CESAR trial, in which 21 (17%) of 126 patients thought to have smouldering multiple myeloma were re-classified as having symptomatic multiple myeloma due to bone disease detected by CT. This is particularly important as misdiagnosed patients, in particular the younger ones, may have received a suboptimal treatment compared with the current standard of care. On the other hand, approximately 15% of patients in the observation group of the QUIREDEX study were free from progression at 7 years; these patients would have received unnecessary therapy if randomised to the experimental group. These results suggest inappropriate management of a third of the patients. In the ECOG-E3A06 study, the benefit of early intervention with lenalidomide was only evident in the high-risk subgroup, which included only 82 patients. Finally, there was no consistency on the definition of high-risk smouldering multiple myeloma between the two studies.

Another important point of debate is what is the most appropriate strategy to pursue in this setting: disease control with a gentler immunomodulating approach based on lenalidomide or a monoclonal antibody to delay progression, or an intensive three or four drug approach followed by hematopoietic stem cell transplantation with curative intent.

This decision is particularly important considering both the short-term toxicity during therapy and the long-term effects of chemotherapy, such as risk of developing second primary malignancies with lenalidomide.

In conclusion, the lack of a standardised and validated definition of high-risk smouldering multiple myeloma, the limitations of the clinical trials done so far, and the absence of a clear management strategy (disease control versus cure) in this setting suggest that early intervention in smouldering multiple myeloma is not ready to become clinical practice yet.

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CONFLICTS OF INTEREST

MB has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and AbbVie; has received research funding from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and Mundipharma.

RM has received honoraria from Amgen, Celgene and Janssen.