

Editorial

Smoldering (asymptomatic) Multiple Myeloma: Cure-versus-control Debate

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Overview

Smoldering (asymptomatic) multiple myeloma (SMM) was first described in 1980 by Kyle and Greipp. SMM is a diagnosis largely based on laboratory findings and represents an intermediate clinical stage between monoclonal gammopathies (MGUS) and multiple myeloma (MM) [1].

At the end of 2014, International Myeloma Working Group (IMWG) updated the definition of SMM as a plasma cell disorder characterized by serum monoclonal protein (IgG or IgA) ≥ 3 g/dL or urinary monoclonal protein ≥ 500 mg per 24 h and/or clonal bone marrow plasma cells (BMPC) 10% to 60% with absence of myeloma defining events or amyloidosis [2].

According to this recent update, asymptomatic patients with BMPCs $\geq 60\%$, involved/uninvolved serum-free light-chain (FLC) ratio > 100 and those with one or more focal lesions of the skeleton by MRI should be considered as MM patients because they have an ultra-high risk of progression to MM (80% to 90% at 2 years) [2].

Most genetic lesions typical of MM are already present in both MGUS and SMM patients. The most important difference between these three clinical entities is the number of clonal plasma cells (PCs) with genetic abnormalities, which increases from MGUS to MM, suggesting a clonal expansion [3].

The median age of the patients at diagnosis ranges from 65 to 70 years [4]. It has been estimated that it represents 8% to 20% of all patients with MM [5].

Diagnostic work-up

Initial investigation of patients with suspected SMM is the same used to diagnose symptomatic MM: CBC, creatinine, calcium, serum quantitative immunoglobulins, serum and urine protein electrophoresis, 24-h proteinuria, immunofixation in serum and urine, sFLC and their ratio [2]. Evaluation of PCs infiltration in either conventional bone marrow aspirate or biopsy is mandatory [6]. All patients should undergo whole-body MRI or PET/CT to discern active lesion if skeletal survey is negative [7]. FISH analysis is not mandatory, but it is highly recommended for all newly diagnosed patients [6].

Risk Factors for Progression

Based on the retrospective data from Mayo clinic, on average, the risk of progression to symptomatic MM is 10% per year for the first five years. Thereafter, the risk goes down to around 3% per year for the subsequent five years. After 10 years of follow up, risk of progression from SMM to MM is similar to that of MGUS (~1% risk per year on average) [8].

SMM represents a heterogeneous clinical entity where a subset of patients have a very indolent course of disease that mimics an MGUS-like state, whereas others have a more aggressive course of disease that has been described as CRAB negative myeloma. There are currently no molecular factors to differentiate these 2 clinically and biologically distinct entities of patients [9].

The size of the serum monoclonal protein, the number of BMPCs [10], immunophenotyping, immunoparesis (i.e. a decrease in one or two of the uninvolved immunoglobulins to 25% below the lowest normal value) [11], serum FLC [12, 13, 14] and the presence of t(4;14), deletion 17p, +1q and hyperdiploidy by FISH analysis have been described to predict risk of progression to symptomatic MM [15]. Gene expression profile may be of benefit in predicting the risk of progression [16]. Other factors to consider: IgA isotype, abnormal MRI, proteinuria, high proliferative rate of PCs in the bone marrow and high circulating plasma cells ($> 5 \times 10^6/L$) [17, 18].

Two risk stratification models predict the progression from SMM to MM. i) the Mayo Clinic model which uses percentage of BMPCs, serum M-protein and FLC ratio [8, 12]. ii) the Spanish PETHEMA classifications which uses immunoparesis and greater than 95% abnormal plasma cells including decreased CD38 expression, expression of CD56 and absence of CD19 and/or CD45 [19].

SMM patients with 1 risk factor of Mayo Clinic or 0 factor of PETHEMA had a 25% risk of developing MM at 5 years (low risk) and patients with 2 factors of Mayo Clinic or 1 factor of PETHEMA had 50% risk of progression at 5 years of follow up (intermediate risk). SMM patients with 3 factors of Mayo Clinic and 2 factors of PETHEMA had over 75% risk at 5 years (high risk). About 20-30% of SMM are high risk [9].

New risk models that incorporate new clinical and biologic features are emerging [11,12, 16, 20].

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Surveillance/Follow-up Tests for SMM

The follow-up of these patients depends on their risk factors for progression. The 2010 IMWG guidelines indicated that patients should be seen every 2 to 3 months for the first year, followed by every 4 to 6 months for 1 year with eventual 6 to 12-month evaluations if clinically stable thereafter [10].

The serum and urine M-component, hemoglobin, calcium, and creatinine levels, Bence Jones proteinuria in the 24-hour urine sample should be reevaluated. Bone survey is recommended annually or as clinically indicated [7]. CT and MRI were equally sensitive, and thus either test can be used [2]. Bone marrow aspiration and biopsy are recommended as clinically indicated [7]. By virtue of FDG uptake, low-level smoldering myeloma is consistently negative on the PET scan [21].

Multiparameter flow cytometry is a newly available tool that measures abnormal cells in the bone marrow and provides information regarding the risk of progression to active myeloma [19, 22].

Treatment

The current standard of care in SMM is observation with close follow-up without chemotherapy until symptomatic disease occurs [6]. Patients defined as having high risk SMM are candidates for clinical trials investigating the value of early therapy (23). In the past, some trials used melphalan to evaluate the effect of early treatment on patients with SMM. It caused obvious toxicity and failed to show a significant benefit [24, 25, 26]. Bisphosphonates as single agents have been studied. Although a reduction in the incidence of skeletal-related events have been noted using pamidronate or zoledronic acid, survival advantage was not shown [27]. With the introduction of novel agents, investigators attempted early treatment with thalidomide, but it did not result in improved survival benefit [28, 29, 30, 31]. In Mateos et al study [32], early treatment of high-risk SMM, with lenalidomide plus low dose dexamethasone, as compared with observation, resulted in a delay in progression to symptomatic disease and an increase in overall survival. However, there are some concerns regarding the generalizability of the Mateos et al trial because 40% of the patients in the trial were included on the basis of flow-cytometry criteria, which are not widely available [33]. Promising results have been reported for the combination of lenalidomide plus dexamethasone with the novel proteasome inhibitor carfilzomib in a series of 12 high-risk patients with SMM. All treated patients achieved a CR and 92% were negative for minimal residual disease by multi-color flow cytometry, with a manageable safety profile [34]. Promising results obtained with a cancer vaccine PVX-410, in a Phase I/II dose-escalation trial, it is now given in association with lenalidomide. This therapy could reinforce the quality of response and improve the outcome, due to a synergistic effect of these two compounds with immunomodulatory properties [35]. Agents being tested include novel immunotherapies such as the Signaling Lymphocytic Activation Molecule family member 7 targeting agent elotuzumab, CD38 targeting antibodies, and programmed cell

death-1 targeting antibodies among others [9]. Some phase II trials are ongoing to determine whether the use of siltuximab (anti-IL-6 mAb), elotuzumab, MLN9708 (ixazomib), or BHK880 (anti-DKK1 neutralizing Ab) is active in high-risk SMM. The results will help provide more evidence and effective strategy to early treatment for patients with high-risk SMM [36].

References

1. Kyle RA, Greipp PR (1980) Smoldering multiple myeloma. *N Engl J Med* 302:1347-1349.
2. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, et al. (2014) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 15(12): e538-548.
3. Mateos MV (2014) Advances in the management of asymptomatic myeloma. *Curr Opin Oncol* 26(6):670-676.
4. Blade J, Dimopoulos M, Rosinol L, Rajkumar SV, Kyle RA (2010) Smoldering (asymptomatic) multiple myeloma: current diagnostic criteria, new predictors of outcome and follow-up recommendations. *J Clin Oncol* 28: 690-697.
5. Dispenzieri A, Stewart AK, Chanan-Khan A, Rajkumar SV, Kyle RA, et al. (2013) Smoldering multiple myeloma requiring treatment: time for a new definition? *Blood* 122(26):4172-4181.
6. Gentile M, Offidani M, Vigna E, Corvatta L, Recchia AG, et al. (2015) Smoldering multiple myeloma: to treat or not to treat. *Expert Opinion on Pharmacotherapy* 16(6): 785-790.
7. National Comprehensive Cancer Network. NCCN Clinical practice guidelines in oncology. Multiple myeloma. Version 2.2016.
8. Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, et al. (2007) Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med* 356(25): 2582-2590.
9. Ghobrial IM, Landgren O (2014) How I treat smoldering multiple myeloma. *Blood* 124 (23): 3380-3388.
10. Kyle RA, Durie BG, Rajkumar SV, Landgren O, Blade J, et al. (2010) Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. *Leukemia* 24(6):1121-1127.
11. Pérez-Persona E, Mateo G, García-Sanz R, Mateos MV, de Las Heras N, et al. (2010) Risk of progression in smoldering myeloma and monoclonal gammopathies of unknown significance: comparative analysis of the evolution of monoclonal component and multiparameter flow cytometry of bone marrow plasma cells. *Br J Haematol* 148 (1): 110-114.
12. Dispenzieri A, Kyle RA, Katzmann JA, et al. (2008) Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood* 111(2):785-789.
13. Larsen JT, Kumar SK, Dispenzieri A, Kyle RA, Katzmann JA, Rajkumar SV (2013) Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma. *Leukemia* 27(4): 941-946.
14. Kastritis E, Terpos E, Moulouopoulos L, Spyropoulou-Vlachou M, Kanellias N, et al. (2013) Extensive bone marrow infiltration and abnormal free light chain ratio identifies patients with asymptomatic myeloma at high risk for progression to symptomatic disease. *Leukemia* 27(4): 947-953.

15. Neben K, Jauch A, Hielscher T, Hillengass J, Lehners N, et al. (2013) Progression in smoldering myeloma is independently determined by the chromosomal abnormalities del(17p), t(4;14), gain 1q, hyperdiploidy, and tumor load. *J Clin Oncol* 31:4325-4332.
16. Dhodapkar MV, Sexton R, Waheed S, Usmani S, Papanikolaou X, et al. (2014) Clinical, genomic and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120). *Blood* 123(1):78-85.
17. Landgren O (2013) Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: biological insights and early treatment strategies. *Hematology (Am Soc Hematol Educ Program)* 2013:478-487.
18. Agarwal A, Ghobrial IM (2013) Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: a review of the current understanding of epidemiology, biology, risk stratification, and management of myeloma precursor disease. *Clin Cancer Res* 19 (5): 985-994.
19. Pérez-Persona E, Vidriales MB, Mateo G, García-Sanz R, Mateos MV, et al. (2007) New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. *Blood* 110(7): 2586-2592.
20. Fernández de Larrea C, Isola I, Cibeira MT, Rosiño L, Calvo X, et al. (2014) Smoldering multiple myeloma: impact of the evolving pattern on early progression. *Blood* 124: (suppl; abstr 3363).
21. Durie B, Waxman A, D'Agnolo A, Williams CM (2002) Whole-body (18) FFDG PET identifies high-risk myeloma. *J Nucl Med* 43: 1457-1463.
22. Ocqueteau M, Orfao A, Almeida J, Bladé J, González M, et al. (1998) Immunophenotypic characterization of plasma cells from monoclonal gammopathy of undetermined significance patients. Implications for the differential diagnosis between MGUS and multiple myeloma. *Am J Pathol* 152:1655-1665.
23. Rajkumar SV, Landgren O, Mateos MV (2015) Smoldering multiple myeloma. *Blood* 125 (20): 3069-3075.
24. Hjorth M, Hellquist L, Holmberg E, Magnusson B, Rodjer S, et al. (1993) Initial versus deferred melphalan-prednisone therapy for asymptomatic multiple myeloma stage I—a randomized study. Myeloma Group of Western Sweden. *European Journal of Haematology* 50 (2): 95-102.
25. Riccardi A, Ucci G, Luoni R, Brugnatelli S, Mora O, et al. (1994) Treatment of multiple myeloma according to the extension of the disease: a prospective, randomized study comparing a less with a more aggressive cytostatic policy. *Br J Cancer* 70 (6): 1203-1210.
26. Riccardi A, Mora O, Tinelli C, Valentini D, Brugnatelli S, et al. (2000) Long-term survival of stage I multiple myeloma given chemotherapy just after diagnosis or at progression of the disease: a multicentre randomized study. Cooperative Group of Study and Treatment of Multiple Myeloma. *Br J Cancer* 82 (7): 1254-1260.
27. Musto P, Petrucci MT, Brinchen S, Guglielmelli T, Caravita T, et al. (2008) A multicenter randomized clinical trial comparing zoledronic acid versus observation in patients with asymptomatic myeloma. *Cancer* 113(7):1588-1595.
28. Rajkumar SV, Gertz MA, Lacy MQ, Dispenzieri A, Fonseca R, et al. (2003) Thalidomide as initial therapy for early-stage myeloma. *Leukemia* 17(4): 775-779.
29. Barlogie B, van Rhee F, Shaughnessy JD, Epstein J, Yaccoby S, et al. (2008) Seven-year median time to progression with thalidomide for smoldering myeloma: partial response identifies subset requiring earlier salvage therapy for symptomatic disease. *Blood* 112 (8): 3122-3125.
30. Weber D, Rankin K, Gavino M, Delasalle K, Alexanian R (2003) Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. *J Clin Oncol* 21(1): 16-19.
31. Witzig TE, Laumann KM, Lacy MQ, Hayman SR, Dispenzieri A, et al. (2013) A phase III randomized trial of thalidomide plus zoledronic acid versus zoledronic acid alone in patients with asymptomatic multiple myeloma. *Leukemia* 27(1): 220-225.
32. Mateos MV, Hernández MT, Giraldo P, de la Rubia J, de Arriba F, et al. (2013) Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med* 369: 438-447.
33. Kristinsson SY, Holmberg E, Blimark C (2013) Treatment for High-Risk Smoldering Myeloma. *N Engl J Med* 369(18): 1762-1763.
34. Landgren O, Roschewski M, Mailankody S, Kwok M, Manasanch EE, et al. (2014) Carfilzomib, lenalidomide and dexamethasone in high risk smoldering multiple myeloma: final results from the NCI phase 2 pilot study. *Blood (ASH Annual Meeting Abstracts)* 124(21): abstract 4746.
35. Wang M, Nooka AK, Yee AJ, Thomas SK, O'Donnell E, et al. (2014) Initial results of a phase 1/2 a, dose escalation study of PVX-410 multi-peptide cancer vaccine in patients with smoldering multiple myeloma. *Blood (ASH Annual Meeting Abstracts)* 124(21):abstract 4737.
36. Tajeja N, Manasanch EE, Korde N, Kwok M, Mailankody S, et al. (2014) Smoldering multiple myeloma: present position and potential promises. *European Journal of Haematology* 92(1):1-12.