

Mini Review

Smoldering Multiple Myeloma: A New Story to Tell

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Abstract

Smoldering Multiple Myeloma (SMM) is characterized by an M spike of 3 g/dL or more and/or a bone marrow containing at least 10% plasma cells with no evidence of end organ damage. Historically management of SMM patients has been based on a “watch and wait” strategy, but after understanding the heterogeneity of the behavior of this disease, several objections have been raised regarding need to start a therapy in some patients.

The identification of several risk factors associated with a risk of progression of approximately 80% within 2 years of diagnosis, has allowed the identification of a small sub-category of SMM patients who gain benefit from early treatment. However, for all other patients, to date, a no-intervention approach is still recommended outside clinical trials. In this review, we provide an overview of SMM including definitions, current diagnostic work-up, risk factors associated with progression, and data from clinical trials performed with the objective of providing early treatment to SMM patients.

Keywords: Smoldering multiple myeloma; Prognosis; Risk-stratification; Treatment of high-risk smoldering myeloma

Introduction

Smoldering Multiple Myeloma (SMM) is a clinical entity initially recognized by Kyle and Greipp in 1980. The authors described six patients presenting Multiple Myeloma (MM) criteria, but who did not show an aggressive disease course [1]. Subsequently, the International Myeloma Working Group (IMWG) defined SMM as a plasma cell disorder characterized by the presence of ≥ 3 g/dL serum M-protein and/or $\geq 10\%$ Bone Marrow Plasma Cells (BMPC), and the absence of end-organ damage such as hypocalcaemia (serum calcium ≥ 11.5 mg/dL), renal insufficiency (serum creatinine ≥ 2 mg/dL), anemia (hemoglobin value below the lower limit of normal by >2 g/dL or hemoglobin value <10 g/dL), and lytic bone lesions (CRAB features) [2]. Finally, Kyle and Rajkumar clarified that the M-protein needed to be of the IgG or IgA subtype and that the BMPCs must be clonal [3]. SMM differs from indolent MM, an asymptomatic disease but with evidence of minimal end-organ damage [3]. Kristinsson et al., evaluating the Swedish Myeloma registry, showed that 14% of newly diagnosed MM patients had SMM [4]. The Mayo Clinic group, analyzing data of 276 SMM patients, showed the annual risk of progression to symptomatic MM was 10% per year for the first 5 years, 5% per year during the subsequent 5 years, and 1% per year after the 10th year [5]. Thus, SMM represents an intermediate clinical stage between Monoclonal Gammopathy of Undetermined Significance (MGUS) and MM. This observation was confirmed by genetic studies, in which it has been demonstrated that most genetic lesions typical of MM are already present in both MGUS and SMM patients. Accordingly, a multistep model of progression, starting with MGUS and transformation to MM, has been proposed. The most important difference between these three clinical entities is the number of clonal PCs with genetic abnormalities, which increases from MGUS to MM, suggesting a clonal expansion [6].

Diagnostic Work-Up

The diagnostic work-up of patients with suspected SMM is the

same used to diagnose symptomatic MM (Table 1) [7]. The gold standard for the evaluation of bone disease remains the skeletal survey; however the IMWG consensus highly recommends that spine and pelvis Magnetic Resonance Imaging (MRI) studies be performed for this category of patients, with the aim of detecting occult lesions not visible with the more conventional skeletal survey [7]. In the setting of SMM patients the role of ^{18}F -fluorodeoxyglucosePET/CT is currently under investigation. Evaluation of PC infiltration is mandatory in the case of bone marrow aspirate/biopsy. Flow cytometry or FISH analysis are not mandatory, but can help to estimate the risk of progression towards active MM. The follow-up includes the evaluation of the monoclonal component, as well as hemoglobin, calcium, and creatinine levels every 3-4 months; however the frequency of follow-up should be adapted according to the patient's risk of progression to symptomatic MM.

Risk Factors Predicting Progression to MM

Many patients with SMM progress to symptomatic MM and need to start therapy. Since the risk of progression for this disease is not uniform over time [5], several studies have been conducted with the aim of recognizing predictive factors and thus of evaluating the risk of progression. Kyle et al. evaluated a large cohort of 267 SMM patients and considering M-protein size and BMPC infiltration, identified three subgroups with a statistically different risk of progression: Group 1, with ≥ 3 g/dL of M-protein and $\geq 10\%$ of BMPCs, with a median Time To Progression (TTP) to symptomatic MM of 2 years; Group 2, with ≤ 3 g/dL of M-protein and $\geq 10\%$ of BMPCs with a median TTP of 8 years; and Group3, with ≥ 3 g/dL of M-protein and $<10\%$ of BMPCs, with a median TTP of 19 years [5]. Moreover, evaluating the same patient population, the Mayo Clinic group showed that the addition of a serum Free Light-Chain (FLC) ratio of <0.125 or >8 to the above-mentioned criteria was associated with an increase in the progression risk to active MM [8]. Subsequently, Larsen et al. showed that SMM cases with an extreme ratio of

Table 1: Diagnostic work-up for SMM patients.

1. History and physical Examination	
	Hemogram with differential and peripheral blood smear review
	Chemistry panel, including calcium and creatinine
2. Routine Testing	Serum protein electrophoresis (serum M-protein) and immunofixation
	24-h urine collection for proteinuria, electrophoresis (urine M-protein) and immunofixation
	Serum-free light-chain measurement (free light-chain ratio)
3. Bone marrow aspirate ± biopsy: infiltration by clonal plasma cells, flow cytometry and FISH analysis	
4. Imaging	Skeletal survey
	MRI of thoracic and lumbar spine and pelvis; ideally, whole-body MRI

involved *versus* uninvolved serum FLC >100, are associated with shorter TTP (median of 15 months) [9]. Furthermore, the Salamanca group demonstrated that both the immunoparesis (a decrease in one or two of the uninvolved immunoglobulin's to 25% below the lowest normal value), and the presence of ≥95% of phenotypically aberrant BMPCs (namely, PCs with over expression of CD56 and CD19, CD45-negative and/or decreased reactivity of CD38 evaluated by multi parameter flow cytometry) were predictive factors for TTP [10]. Based on these two parameters, the same group proposed a scoring system to stratify SMM patients: cases with both risk factors had a median TTP of 23 months, cases with one risk factor of 73 months, while median was not reached in cases with none of two risk factors [11]. Moreover, the Mayo Clinic group showed 21 out of 655 SMM cases with BMPCs >60% had a progression risk of 95% at 2 years [12]. The same group showed that high levels of circulating PCs (>5 × 10⁶/L and/or >5% BMPCs per 100 cytoplasmatic immunoglobulin-positive mononuclear cells) correlated with a shorter TTP (progression risk of 71% at 2 years) [13]. On the basis of the pattern of evolution of the M-protein during the clinical course we may identify two types of SMM: the evolving cases, characterized by a progressive increase in M-protein and the non-evolving cases with stable M-protein that abruptly increases when patients develop active MM. Rosinol et al. showed evolving cases had a shorter TTP than the non-evolving cases (median of 1.3 vs 3.9 years) [14]. Similarly, the Southwest Oncology Group showed that SMM patients with an increase in M-protein to

≥3 g/dL over a 3-month period had a progression risk of 33.3% at 2 years [15]. Neben et al., analyzing data of 249 SMM patients, showed that the presence of t (4;14), deletion 17p, +1q and hyperdiploidy by FISH analysis shortened the TTP independent of tumor burden in SMM cases [16]. Rajkumar et al. confirmed that t (4;14) and del(17p) negatively impacted on TTP in an independent series of 351 SMM cases [17]. In addition, the Southwest Oncology Group showed that using a 70-gene signature it is possible to prognostically stratify SMM cases [15]. Instead, the German group reported that SMM patients with >1 focal lesion on whole-body MRI had a higher risk of progression to active MM: 70% after 2 years [18]. Moreover, a recent study showed that the increase in the number and/or size of focal lesions in follow-up MRI of SMM patients also had a predictive value for TTP [19]. Based on the presence of these prognostic factors we can stratify SMM patients and identify cases at elevated risk of progression (Table 2). Among these, a subgroup of cases has been identified and defined as “ultra-high risk” patients, those who have a ≥80% probability of progression at 2 years. According to the new IMWG guidelines ultra-high risk patients should be considered cases with active MM and treated immediately, before the development of MM-related symptomatology [7].

Therapeutic Approach to SMM

As stated above, smoldering multiple myeloma is a heterogeneous clinical entity and it includes patients with an indolent disease and

Table 2: Biomarkers for the identification of SMM at elevated risk of progression to symptomatic MM.

SMM patients at ultra-high risk (≥80% of progression risk at 2 years)
Biomarkers for the identification of this subset of patients: the presence of one of the following
1) Involved/uninvolved serum free light-chain ratio >100;
2) ≥60% of clonal plasma cells in bone marrow biopsy;
3) >1 focal lesion plus diffuse pattern in whole-body MRI;
SMM patients at high risk (50-79% of progression risk at 2 years)
Biomarkers correlated with tumor burden: 1+2 or 1+2+3
1) ≥10% clonal plasma cell bone marrow infiltration;
2) ≥3 g/dL of serum M-protein;
3) Serum-free light chain ratio > 0.125 or <8;
Biomarkers correlated with immune phenotyping characterization and immunoparesis: 1+2
1) >95% of aberrant bone marrow plasma cells measured by flow cytometry;
2) 25% decrease in one or both uninvolved immunoglobulins with respect to the lowest normal value;
Biomarkers correlated with primary molecular cytogenetic abnormalities and GEP signature: the presence of one of the following
1) t(4;14);
2) del17p;
3) +1q24;
4) Hyperdiploidy;
5) GEP-70 risk;
Biomarkers correlated with levels of peripheral blood circulating plasma cells: the presence of one of the following
1) Absolute peripheral blood PCs >5000 ×10 ⁶ /L;
2) >5% cytoplasmic Ig positive PCs per 100 mononuclear cells;

Table 3: Trials including conventional chemotherapy and bisphosphonate as single agent in SMM.

	Hjorth [23]	Riccardi [24]	D'Arena [25]	Musto [26]
Disease	SMM and IMM	DSS Stage I MM	SMM	SMM
Phase	RCT	RCT	RCT	3
Treatment	Early MP vs. deferred MP	Early MP vs. deferred MP	Pamidronate vs. observation	Zoledronic acid vs. observation
No patients	25 vs. 25	75 vs. 70	89 vs. 88	81 vs. 82
Response \geq PR (%)	52 vs. 55	40 vs. 55	NA	NA
Follow-up (months)	48	65	5 yrs	NA
TTP (months)	NR vs. 12	NA	46 vs. 48	67 vs. 59
SREs (%)	NA	NA	39 vs. 72.7 (p=0.009)	55 vs. 78 (p=0.04)
OS (months)	52 vs. 53	64 vs. 71	Not different	Not different

Abbreviations: IMM: Indolent Multiple Myeloma; DSS: Durie-Salmon Stage; RCT: Randomized Controlled Trial; MP: Melphalan Plus Prednisone; NA: Not Applicable; Sres: Skeletal Related Events; NR: Not Reached

Table 4: Trials including new drugs in SMM.

	Rajkumar [27], Detweiler-Short [28]	Barlogie [29]	Witzig [30]	Mateos [21,22]
Disease	SMM and IMM	SMM	SMM	HR SMM
Phase	2	2	3	3
Treatment	Thal	Thal + PAM	Thal + ZLD vs. ZLD	RD vs. observation
No patients	29	76	35 vs. 33	57 vs. 62
Response \geq PR (%)	34	25	37 vs. 0	90 (CR: 26; sCR: 12)
Follow-up (months)	10.2 yrs	6 yrs	5.9 yrs	64
TTP (months)	35	60% at 4 yrs	2.4 yrs vs. 1.2 yrs (p=0.02)	NR vs. 21 (<0.0001)
OS (months)	49	91% at 4 yrs	Not different	5-year OS: 93 vs. 67 (p=0.008)
Grade 3-4 toxicity (%)				
Hematologic	3	7	20 vs. 6	9 vs. 0
Infection	13	NA	0	6 vs. 0
Peripheral neuropathy	14	8	0	0
Cardiac	7	7	0	0
DVT	NA	0	3 vs. 3	0

Abbreviations: HR: High Risk; Thal: Thalidomide; PAM: Pamidronate; ZLD: Zoledronic Acid; RD: Lenalidomide Plus Dexamethasone; PR: Partial Remission; CR: Complete Remission; Scr: Stringent Complete Remission; TTP: Time To Progression; NR: Not Reached; OS: Overall Survival; NA: Not Applicable; DVT: Deep Venous Thrombosis.

those with a sudden evolution to symptomatic myeloma. Moreover, no variable is currently able to identify those patients who will progress to malignancy with certainty and significant discrepancies have been found between the Mayo Clinic [8] and the Spanish Pethema [10] models, showing a rate of agreement of only 28.6% [20]. The current strategy adopted for management of SMM patients is to observe patients until the development of CRAB features or non-CRAB end-organ damage (i.e. hyper viscosity and a myeloid light-chain (AL) amyloidosis) or extramedullary plasmocytoma. Only recently has a randomized study shown that early treatment significantly prolongs survival of high-risk SMM patients [21,22]. Two small controlled trials conducted in the 1990s comparing early treatment with melphalan plus prednisone with observation did not show any survival advantage [23,24]. In subsequent years, neither pamidronate nor zoledronic acid treatment demonstrated a change in the natural history of SMM when compared with observation only patients [25,26]. The introduction, starting in the 2000s, of more active agents such as thalidomide revived the possibility of treatment of the early stages of MM. In a phase II study including 29 patients with

SMM, thalidomide administered at dose of 200 mg/day (escalated to the maximum dose of 800 mg/day) induced an ORR in 34% of patients and, after a median follow-up of 10.2 years, the median TTP and OS were 35 and 49 months, respectively, with adverse events relevant enough to induce the authors to not recommend the use of thalidomide for SMM [27,28]. Thalidomide (200 mg/day) was combined with monthly pamidronate in another phase II study showing that the achieving of PR or better on thalidomide therapy was the only parameter significantly and independently associated with short time to MM therapy, thus suggesting a rapid development of resistance clones or tumor escape after drug discontinuation [29]. In a phase III trial comparing thalidomide (200 mg/day) plus zoledronic acid (4 mg monthly) versus zoledronic acid alone in 68 patients, no significant prolongation of TTP was seen in patients in the 2 drug-arm compared with those treated with only bisphosphonates (4.3 vs. 3.3 years respectively) similarly to OS (74% vs. 73% at 5 years). However the tolerability to treatment was different, with 11 patients discontinuing therapy due to adverse events in the thalidomide-zoledronic acid vs. only 1 with zoledronic acid as

Table 5: Most relevant ongoing trials in patients with SMM.

Phase 2/3:	Lenalidomide or observation in treating patients with asymptomatic high-risk smoldering multiple myeloma (NCT01169337)
Phase 2:	Zoledronic acid in the management of patients with asymptomatic/early stage multiple myeloma (NCT0026151)
Phase 2:	effect of low dose bortezomib on bone formation in smoldering myeloma patients (NCT00983346)
Phase 2:	Carfilzomib, lenalidomide and dexamethasone for smoldering multiple myeloma (NCT01572480)
Phase 2:	Trial of combination of elotuzumab and lenalidomide± dexamethasone in high-risk smoldering multiple myeloma (NCT02279394)
Phase 2:	A study to evaluate 3 dose schedules of daratumumab in participants with smoldering multiple myeloma (NCT02316106)
Phase 2:	A study of siltuximab (anti-IL6 monoclonal antibody) in patients with high-risk smoldering multiple myeloma (NCT01484275)
Phase 2:	A phase II study of BI-505 in smoldering multiple myeloma (NCT01838369)
Phase 2:	study on the anti-tumor activity, safety and pharmacology of IPH2101 in patients with smoldering multiple myeloma (KIRMONO) (NCT01222286)
Phase 2:	Study of BHQ880 in patients with high-risk smoldering multiple myeloma (NCT01302886)
Phase 2:	A phase II trial of anti-KIR in smoldering multiple myeloma (NCT01248455)
Phase 2:	Anakirna with or without dexamethasone in treating patients with smoldering or indolent multiple myeloma (NCT00635154)
Phase 2:	Phase II study to evaluate fenofibrate therapy in patients with smoldering or symptomatic multiple myeloma (NCT01965834)
Phase 2:	A trial of TBL-12 sea cucumber extract in patients with untreated asymptomatic myeloma (NCT01302366)
Phase 2:	Green tea extract in treating patients with monoclonal gammopathy of undetermined significance and/or smoldering multiple myeloma (NCT00942422)
Phase 1:	Phase 1/2a study of cancer vaccine to treat smoldering multiple myeloma (NCT01718899)

the single agent [30]. For the first time in the history of SMM, the Spanish Myeloma Group conducted a randomized trial in selected high-risk patients, comparing lenalidomide plus dexamethasone with observation. High-risk disease was defined as BMPC infiltration of at least 10% and a M-protein (IgG \geq 3 g/dL, IgA \geq 2 g/dL, or urine Bence Jones protein $>$ 1 g per 24 hours), or only one of the two criteria described above and \geq 95% phenotypically abnormal PCs and the presence of immunoparesis (decrease in 1 or 2 of the uninvolved immunoglobulin's of more than 25% compared with normal range). Patients received 9 cycles of lenalidomide (25 mg) on days 1–21 and dexamethasone (20 mg) on days 1–4 and days 12–15 of a 28-day cycle, followed by maintenance therapy with lenalidomide (10 mg) on days 1–21 of a 28-day cycle for two years. Early treatment yielded a higher overall response rate, a significant delay in the time to progression to symptomatic disease, and a benefit in survival [21]. The median TTP with lenalidomide-dexamethasone, updated after a median follow-up of 64 months, was significantly higher compared to observation (not reached vs. 21 months; hazard ratio, 6.21; $p<.0001$); 5-year OS rate was 93% in the treatment group vs. 67% in the observation arm (hazard ratio, 4.35; $p=.008$) [22]. Although the risk related to the development of a symptomatic disease was clearly higher in non-treated patients (76% vs. 23%), it is notable that 12% of patients experienced serious adverse events in the lenalidomide-dexamethasone arm compared to 3% in the observation group, and 1 patient died of pneumonia [22]. (Tables 3 and 4) summarize the most important trials with conventional and new drugs conducted in patients with SMM. Other studies have identified possible strategies that may allow intervention at an earlier stage to delay or prevent progression. The results of a phase II pilot study have recently been reported indicate encouraging activity of new drug combinations in this setting. The patients were treated with 8 months of induction (28-day cycles of carfilzomib 20/36 mg/m² on days 1, 2, 8, 9, 15, and 16, lenalidomide 25 mg/day days 1-21 and dexamethasone 10 or 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23). Although the number of patients enrolled was very small (n=12), an ORR of 100% has been observed to date, and 92% of patients were negative for minimal residual disease by multi-color

flow cytometry [31]. Among all the novel therapeutic approaches in MM, immunotherapy is probably one of the most promising strategies showing interesting results in preclinical and clinical studies. Thus, it is not surprising that researchers are also testing these compounds in SMM patients. Preliminary data of a phase I/II dose-escalation study with the cancer vaccine, PVX-410 have recently been reported. The vaccine was given intramuscularly with escalating doses (0.4–0.8 mg); a total of six doses were administered over a 10-week period. All treatment-related events were low grade and related to the infusion as expected with vaccinations. In all patients (n=12) a positive immune response was observed and 7 patients achieved a stable disease after a median follow-up of 9 months [32].

Several other trials testing novel drugs and new combination are ongoing for patients with SMM; these are summarized in (Table 5).

Summary and Conclusion

After several attempts there is now a consensus regarding the definition of the subset of patients with SMM in which procrastination of therapy could be considered unreasonable due to the high probability of developing of end-organ damage within 2 years of diagnosis [7]. However, for all other patients outside the category of ultra high-risk MM, the evidence of benefit due to an anti-myeloma therapy is unclear. The rationale of treating SMM is based on the presence, in an early stage of MM, of a lower tumor burden, a lower resistant disease, and a lower probability of a sudden evolution in a symptomatic and often life-threatening disease. Fundamental biological understanding of the mechanisms involved in MM progression is rapidly increasing and the identification of molecularly derived risk factors in the near future will more accurately characterize the risk of transformation of SMM to MM. Moreover, new safe and active agents are now available and it may be difficult to resist the temptation to use them in the setting of SMM. However, these novel anti-myeloma therapies are currently very expensive, not approved as an indication for treatment of SMM and data on long-term toxicities and quality of life are not sufficient. In conclusion, the current standard care for SMM patients

remains observation; however ongoing clinical studies will help clarify whether this approach has to be modified.

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