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MULTIPLE MYELOMA (P KAPOOR, SECTION EDITOR)

Smoldering Multiple Myeloma: Emerging Concepts and Therapeutics

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Abstract Smoldering multiple myeloma (SMM) is a pre-malignant condition with an inherent risk for progression to multiple myeloma (MM). The 2014 IMWG guidelines define smoldering multiple myeloma as a monoclonal gammopathy disorder with serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60 % without any myeloma-defining events or amyloidosis. The risk for progression of SMM to MM vary based on clinical, laboratory, imaging, and molecular characteristics. Observation, with periodic monitoring is the current standard of care for SMM. Over last few years, research advances in SMM have led to the delineation of newer risk factors for progression and identification of a "high-risk" group that would potentially benefit from early treatment. This review focuses on advances in the SMM risk-stratification model and recent clinical trials in this patient population.

Keywords Smoldering myeloma · High-risk smoldering myeloma · Progression related biomarkers · Gene expression profiling · Treatment

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Introduction

Plasma cell dyscrasias range in spectrum from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukemia. Smoldering multiple myeloma (SMM) is a key condition in this continuum. Evident from its name, SMM or asymptomatic myeloma is a precursor of multiple myeloma (MM) and has the potential to transition into symptomatic MM. Importantly, most MM disease states arises from a precursor disease state rather than de novo [1]. The risk of progression from MGUS or SMM to MM varies depending on, type and degree of monoclonal gammopathy, involvement of light chains, underlying cytogenetic abnormalities, molecular gene expression profile, early radiographical findings and the duration of SMM [2••, 3–7]. Based on a small case series, serial exome sequencing at precursor disease time-point (SMM or MGUS) and MM clinical progression time-point in the same patients does not reveal major differences in types of mutations observed but rather the pattern of mutational load may change [8]. The biological evolution from precursor disease to active symptomatic disease state is still unknown.

Immense progress has been made in the treatment of MM with the advent of proteasome inhibitors, immune-modulatory agents directly leading to improved overall survival across most age groups [9]. However, only a limited number of MM patients achieve long-term remission or cure [10]. Access to efficacious and tolerable myeloma therapeutics has led to clinical research exploring initiation of treatment earlier in the natural course of myeloma, specifically SMM. However, it is unclear at this time if such treatment approach would have a meaningful impact with survival benefit or potentially cure myeloma. In this review, we focus on the newer strategies in risk stratification and management of SMM. For details regarding biology and understanding of MGUS we refer the readers to other reviews [3, 11••, 12, 13].

New Definitions

In 2014, the International Myeloma Working Group (IMWG) guidelines [14] re-defined MM as a disorder with clonal bone marrow plasma cells ≥10 % or biopsy-proven bony or extramedullary plasmacytoma and any of the following myeloma-defining events (≥1): (a) evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder (hypercalcemia: serum calcium >1 mg/dL higher than the upper limit of normal or >11 mg/dL, renal insufficiency: creatinine clearance <40 mL/min or serum creatinine >2 mg/dL; anemia: hemoglobin value of 2 g/dL below the lower limit of normal, or <10 g/dL; one or more osteolytic lesions on skeletal radiography, CT, or PET/CT), (b) clonal bone marrow plasma cell percentage ≥60 %, (c) involved: uninvolved serum free light-chain ratio ≥100, and (d) >1 focal lesions on MRI studies. Importantly, compared to the previous 2008 guidelines, the 2014 IMWG definition of MM recognizes that asymptomatic myeloma patients with "ultra high-risk" features (bone marrow plasma cell percentage ≥60 %, involved: uninvolved serum free light-chain ratio ≥100, >1 focal lesions on MRI studies) should no longer wait for end-organ damage to occur before initiating treatment since median time to clinical progression for these individuals is <2 years.

In accordance with the above changes to the MM criteria, the 2014 IMWG guidelines [14] re-defined smoldering multiple myelomas as a monoclonal gammopathy disorder with:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60 %.
- Absence of myeloma-defining events (MDE) or amyloidosis.

MGUS is an asymptomatic condition characterized by serum monoclonal protein <3 g/dL, clonal bone marrow plasma cells <10 % and absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions [14]. The risk of progression of MGUS to MM depends on its subtype (IgG, light-chain and IgM). The progression rate is 1 % per year for non-IgM type, 1–3 % per year for light-chain type and 1-5 % per year for IgM sub-type [14]. In this review we focus our attention on smoldering multiple myeloma biology and management.

Factors Affecting Progression to Multiple Myeloma

Like multiple myeloma, SMM is also a heterogeneic entity with respect to disease activity and the risk of progression varies. In general, while the rate of progression of SMM is higher than MGUS, multiple clinical, biochemical and cytogenetic factors likely affect its progression symptomatic MM. When originally described in a retrospective study by Kyle et al. from the Mayo clinic, 276 patients were identified with the diagnosis SMM and were followed for 2138 cumulative person-years. In this study, the overall risk of progression was noted to be 10 % per year for the first 5 years, 3 % per year for the next 5 years, and 1 % per year for the last 10 years [3]. The cumulative risk of progression of SMM was noted to be 73 % at 15 years and the median time to progression was 4.8 years. Of note, the risk of progression to myeloma decreases as the number of years from diagnosis increases, likely representing the heterogeneic biological activity of SMM. Since the original Kyle papers describing SMM, subsequent studies on risk modeling (Mayo Clinic criteria and the Programa para et Tratamiento de Hemopatias Malignas (PETHEMA) Spanish group criteria) have provided insight into predicting risk of transformation [3, 15] (Fig. 1). Other groups have additively expanded on these risk models to incorporate novel imaging techniques and gene expression profiling. The results are summarized below:

1. Myeloma biomarkers and bone marrow involvement

   Higher M-protein level and marrow plasma cell percentage commonly correlates with faster progression [3]. In the above-mentioned study by Kyle et al., the median time to progression (TTP) for smoldering patients with M-protein <4 g/dL compared to M-protein ≥4 g/dL was 75 months vs. 18 months ($p < 0.001$). In addition, for patients with bone marrow plasma cells percentages <20, 20–50, and >50 %, the median TTP was 117, 26, and 21 months, respectively ($p < 0.001$). Also in this study, the type of monoclonal protein was shown to predict the course of the disease. Patients with IgG monoclonal gammopathy had significantly longer median TTP compared to patients with IgA monoclonal gammopathy (75 vs. 27 months, respectively, $p = 0.01$). The study by Perez-Persona et al. (PETHEMA model) identified the risk for progression based on multi-parameter flow-cytometry analysis of bone marrow plasma cells [15]. The study identified aberrant plasma cells (aPC) based on validated immunophenotypic criteria, i.e., absence of CD19 and/or CD45, decreased expression of CD38, and overexpression of CD56. Patients with high aPCs/ bone marrow plasma cells (BMPC) ratio (≥95 %) at diagnosis had a significantly higher risk of progression in SMM ($p < .001$). Multivariate analysis showed that the percentage aPC/BMPC ≥ 95 % ($p = 0.001$) and immunoparesis ($p = 0.02$) as independent prognostic markers for progression in SMM.

   In 2008, colleagues from the Mayo Clinic built upon these original observations and published a risk model demonstrating that the following groups define independent risk factors for SMM progression to active MM: M-

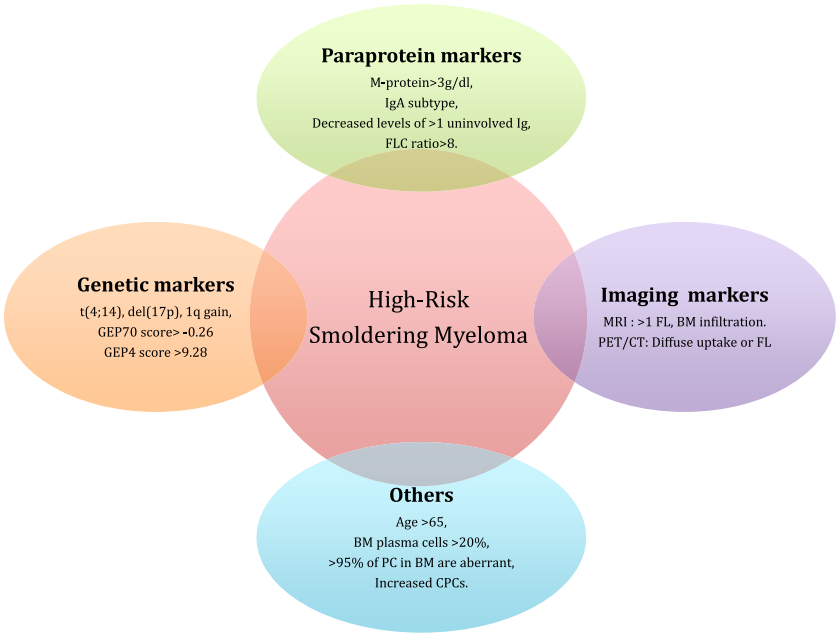

Fig. 1 Factors associated with high-risk smoldering myeloma. *FLC* Free light chain ratio, *IgA* Immunoglobulin A, *BM* bone marrow, *PC* plasma cells, *CPC* circulating plasma cells, *GEP* gene expression profiting

protein ≥ 3 g/dL (HR 1.9 CI 1.4 to 2.6, $p < 0.01$) bone marrow plasma cell percentage ≥10 %(HR 3.1 CI 1.6 to 6.3, $p < 0.01$), and serum free light-chain (FLC) ratio ≤0.125 or ≥8 (HR 1.9 CI 1.3 to 2.7, $p < 0.01$) [16]. The 5-year progression rate for high, intermediate, and low-risk SMM as determined by the above criteria is 76, 51, and 25 %, respectively.

These findings were further validated in more recent prospective observational clinical trials S0120 and a clinical study series from Greece. In the SWOG study, age > 65 [Hazard ratio (HR) 2.10 (CI: 1.19, 3.69), $p = 0.010$], M-protein > 3 g/dL [HR 3.52 (CI: 1.86, 6.65), $p < 0.001$], and bone marrow plasma cells > 20 % [HR 3.22 (CI: 1.77, 5.84), $p < 0.001$] were reported to be strong clinical risk factors associated with progression to myeloma [2••]. Subsequently, researchers from Greece and Mayo Clinic independently identified a group of SMM patients with very high-risk features, including involved to uninvolved FLC ratio ≥100 (HR: 9, CI 2.15 to 39, $p = 0.003$) and bone marrow plasma cell percentage ≥60 %(hazard ratio, HR: 13.7, CI 4.44 to 42.2, $p < 0.001$), that often leads to clinical progression within 2 years [17, 18]. Both of these features are now considered myeloma-defining lesions as noted above.

2. Circulating plasma cells

Circulating plasma cells (CPCs) have been studied as a potential biomarker for disease virulence in plasma cell disorders. CPC have been shown to be an independent predictor for progression in MM, amyloidosis, SMM and MGUS [19–22].

Witzig et al. evaluated 57 SM patients for abnormal circulating peripheral blood mononuclear PCs by immunofluorescence and correlated it with their pattern of progression. They noted that 63 % of patients who progressed (with in 1 year) had abnormal CPCs compared to only 10 % in patients who did not progress [23]. Also, the median TTP for patients with abnormal CPCs was 0.75 years, compared to 2.5 years for patients without abnormal CPCs ($p < 0.01$).

In a more recent study by Bianchi et al., 91 patients with SMM were tested for CPCs by immune-florescent assay. Elevated CPCs was defined as an absolute peripheral blood PCs greater than 5×10^6/L and/or greater than 5 % PCs per 100 cytoplasmic immunoglobulin (Ig)-positive peripheral blood mononuclear cells [22]. Fifteen percent of patients (14 of 91) had elevated CPCs. The 3-year progression rate was significantly higher in the group with elevated CPCs compared to the group without elevated CPCs (86 vs. 34 %, respectively, $p < 0.001$). The median TTP was much shorter in the high CPCs group compared with the group without elevated CPCs (12 vs. 57 months, respectively, $p < 0.001$). Similarly, overall survival (OS) was much shorter in the high CPCs group (49 vs. 148 months, respectively, $p < 0.001$).

3. Gene Expression Profile

The South West Oncology Group S0120 study is a prospective study of patients with symptomatic monoclonal gammopathy (MGUS + Asymptomatic MM or SMM) that evaluated clinical and genomic variables related to progression to symptomatic MM. This study validated a 70-gene expression profiling score (GEP-70) as an independent predictor for progression to symptomatic myeloma. A GEP 70 score >−0.26, along with a serum M-protein >3 g/dL and a serum FLC >25 mg/dL, was

associated with a 70 % 2-year risk of progression to MM requiring therapy in SMM patients. Furthermore, a GEP 70 score >−0.26 alone had a HR of 6.81(2.90–15.97, $p < 0.001$) for progression to MM requiring therapy in SMM patients [2••].

More recently, the S0120 study group published an update on the GEP score for SMM. They further refined the risk GEP prediction model by developing a new genetic signature from differentially expressed genes [24]. They performed gene expression profiling of 105 SMM patients in the Affymetrix platform to identify genetic signatures that confer a high-risk for progression to MM and time to therapy (TTT) for MM. Among the genes analyzed, four genes RRM2 (2p25-p24), DTL (1q32), TMEM48 (1p32.3) and ASPM (1q31) were shown to be predictive of TTT. A binary cut-point was identified for the four gene score and set at 9.28. A total of 14 patients had score >9.28 and 91 patients had score <9.28. The 2-year progression probability was significantly higher in patients with score >9.28 as compared to patients with score <9.28 (85.7 vs. 17.8 %). GEP 4 score >9.28 was a strong risk factor for progression and myeloma therapy [Hazard ratio (HR) 9.36 (CI 4.29–20.4, $p < 0.001$)]. Patients who had a low GEP 4 score (<9.28) along with baseline monoclonal protein <3 g/dL and albumin ≥3.5 g/dL had low-risk smoldering myeloma with a 5.0 % chance of progression at 2 years.

4. Cytogenetic abnormalities

Several studies have looked at cytogenetic abnormalities in patients with asymptomatic myeloma and their role in progression to symptomatic disease. The incidence of specific cytogenetic abnormalities seems to be similar between MGUS and MM. These studies have shown mixed results in terms of risk of progression to symptomatic myeloma. A recent study by Rajkumar et al. studied the cytogenetic abnormalities noted in patients with SM and their clinical implications [5]. In their study with 351 SM patients, trisomies (43.9 %) and immunoglobulin heavy chain (IgH) translocations (36.2 %) were the most common cytogenetic abnormalities. Among the IgH translocations observed, t(4;14) had the worst outcome with shorter TTP and OS compared to other cytogenetic aberrations. Patients were classified into four groups based on their risk for progression. t(4;14) and del(17p) was classified as high-risk, trisomies alone as intermediate-risk, t(11;14), monosomy/del(13q) alone, patients with both IgH translocations and trisomies as standard risk and patients with normal FISH as low-risk. The median TTP was 24 months with t(4;14)/del(17p), 34 months with trisomies alone, 55 months with other abnormalities such as t(11;14), isolated del (13q) and not reached in low-risk group. The median OS was 105 months for t(4;14)/del(17p) compared to 135 month for trisomies alone and 147 months for t(11;14), del(13q) and other aberrations.

Another study by Neben et al. from Germany looked into cytogenetic abnormalities and progression risk in SM [25]. In this study, the high-risk aberrations such as del (17p), t(4;14), and +1q21 were reported to be associated with adverse prognosis in SM with hazard ratios (HRs) of 2.90 (95 % CI, 1.56 to 5.40), 2.28 (95 % CI, 1.33 to 3.91), and 1.66 (95%CI, 1.08 to 2.54), respectively. Interestingly, hyperdiploidy (considered to be favorable prognostic factor in MM) was noted to confer adverse outcome in SMM (HR, 1.67; 95 % CI, 1.10 to 2.54) in this study.

In the prospective SWOG study mentioned above, cytogenetics was not noted to be a significant factor in predicting increased risk in the multivariate analysis.

5. Imaging studies

The quest to identify high-risk SMM and treat them sooner has led to exploring the utility of advanced imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT scan).

Evidence for the role of MRI in prognosticating SM has been known for at least two decades now. A study by Moulopoulos et al. assessed 38 patients with asymptomatic MM and negative skeletal surveys with thoracic and lumbo-sacral spine MRI [26]. In this study, bone marrow involvement was noted in 19/38 patients (50 %). Patients with bone marrow involvement had faster progression of disease with median TTP of 16 months compared to 43 months ($p < 0.01$) in patients with negative MRI scans. Subsequently, Hillengass and colleagues studied the role of whole body MRI (WB- MRI) in 149 patients with asymptomatic MM in detecting focal lesions (FL) and their clinical correlation [27•]. FLs were seen in 28 % of patients. Presence of more than one FL was a strong adverse prognostic factor predicting progression to symptomatic MM (HR 3.01, $p = 0.002$). The median time to progression in the group with >1FL was 13 months compared to median not reached in the group with <1FL.

Similarly, the study by Kastritis et al. showed that abnormal marrow signal of the spine (detected by MRI) was associated with a significant risk of progression (median TTP of 15 months, $p = 0.001$) and extensive BM infiltration >60 % was an independent risk factor for progression to symptomatic MM (HR: 13.7, $p < 0.001$) [17]. The SWOG S0120 study echoed the above findings as well [2••]. The convincing evidence from the above studies on the role of MRI in detecting high-risk SMM has directed the IMWG recommending all patients with SMM or asymptomatic MM to undergo WB- MRI (or spine and pelvic MRI if WB-MRI is not available), and starting therapy if they have more than one focal lesion of a diameter >5 mm [28].

The role for PET/CT scan was relatively less established in identifying high-risk SMM until recently. A recent Mayo Clinic study evaluated 188 patients with SM with PET/CT scan and followed a cohort of 122 (25 PET/CT positive and 97 negative) patients not needing treatment among them [29]. They reported that the probability of progression to MM within 2 years was 75 % in patients with a positive PET/CT group compared with 30 % in patients with a negative PET/CT. Furthermore, the median time to progression was much shorter (21 months) in the PET/CT positive group vs. 60 months in the PET/CT negative group, respectively, $p = 0.0008$. When stratified by the type of lesions, the probability of progression was 87 % at 2 years for patients with evidence of underlying osteolysis and 61 % for patients with abnormal PET/CT uptake but no evidence of osteolysis.

A European study by Zamigni et al. showed that showed similar predictive value for PET/CT scan in identifying high-risk SM [30]. In this study, PET/CT scan was used to identify focal lesions (FL) without underlying osteolysis. Patients with underlying osteolytic lesions were excluded from this study. Among the 120 patients evaluated, PET/CT was positive in 16 % of patients (1 FL in 8 patients, 2 FLs in 3, >3 FLs in 6, and diffuse bone marrow involvement in 2 patients). The risk of progression of those with positive PET/CT was higher [HR 3.00 (95 % CI 1.58–5.69, $p = 0.001$)]. The median TTP was 1.1 years in the PET/CT positive group vs. 4.5 years for PET/CT negative patients.

Treatment Paradigms of Smoldering Myeloma

Clinical researchers have attempted to treat patients with SM hoping that therapeutic intervention at an earlier stage in the natural history of myeloma might alter the disease course and potentially yield long-term remissions. Owing to the advancements in diagnostic studies and change in the IMWG definition of multiple myeloma, some patients who were previously identified as SMM or asymptomatic MM are now diagnosed with symptomatic MM and started on therapy sooner [14]. Also, multiple newer prognostic markers have been identified to risk stratify SM and identify select group of SM patients (high-risk) who are likely to have faster progression [2••, 3, 4, 17, 24, 26, 27•]. However, it is not well established if routine treatment of all patients in the high-risk cohort is indicated to improve treatment outcome and prolong survival. Outside clinical trials, the standard of care for patients with smoldering or asymptomatic myeloma remains observation [31–34]. Multiple drugs including older chemotherapeutic agents, bisphosphonates and novel drugs have been evaluated in treatment of SM.

Older Agents

Studies evaluating regimens such as melphalan-prednisone and vincristine-doxorubicin-dexamethasone for the treatment of smoldering or asymptomatic myeloma have yielded negative results and such approaches have offered no survival advantage [35–37]. Thalidomide, an older immune-modulatory (IMiD) agent has been studied as a single agent in a small single arm phase 2 trials with 31 patients [38]. In this trial, 34 % of patients had a partial response (PR). The median TTP to symptomatic myeloma and median OS were 35 and 86 months, respectively.

Bisphosphonates and Combinations

Single agent bisphosphonates (pamidronate and zoledronic acid) have been studied in randomized controlled trials (RCT) compared with observation for patients with SM [39, 40]. Both trials showed that bisphosphonate alone decreased skeletal events, but did not alter disease course, progression or survival.

The combination of thalidomide and bisphosphonates has been evaluated as well in SMM. In a phase 2 study, Barlogie et al. treated 76 SMM patients with thalidomide and pamidronate [41]. The 4-year EFS and OS in this study was 60 and 91 %, respectively. Significant adverse effects were noted in this study with 86 % of patients needing thalidomide dose modification and 50 % needing cessation. Patient who achieved a partial response (PR) had inferior event free survival than the patients with just trial defined improvement (IMP) of markers or no response. A phase 3 RCT by Witzig et al. evaluated the combination of thalidomide (thal) and zoledronic acid (ZLD) compared to ZLD alone in patients with asymptomatic MM [42]. The median TTP was higher for Thal/ZLD patients compared with ZLD alone (2.4 vs. 1.2 years; HR, 2.05; 95 % CI: 1.1–3.8; $p = 0.02$). And, after 1 year 86 % of Thal/ZLD patients were progression free compared with 55 % on ZLD alone ($p = 0.0048$). Although antitumor response was observed with the addition of Thal to standard ZLD, no overall survival benefit was evident with the doublet, and the study was prematurely closed due to slow accrual rate.

Newer Agents

Lenalidomide (a newer IMiD) in combination with dexamethasone (Rev/Dex) vs. observation was evaluated in a phase 3

RCT in patients with high-risk SMM by Mateos et al. [43••]. With a median follow-up of 40 months, the median TTP was much longer in the treatment group than in the observation group (median not reached vs. 21 months; HR for progression, 0.18; 95 % CI, 0.09 to 0.32; $p < 0.001$). Also, this was the first study to show an improvement in OS in patients with SMM with 3-year survival rate in treatment arm significantly higher than observation (94 vs. 80 %; HR, 0.31; 95 % CI, 0.10 to 0.91; $p = 0.03$). To date, this is the only trial in selected asymptomatic myeloma patients to show an improvement in overall survival by early intervention. In 2015, Korde and colleagues, reported results on a pilot study using carfilzomib, lenalidomide, and dexamethasone in 12 high-risk SMM patients demonstrating 100 % ≥ near complete response (nCR) rate with 11/12 (92 %) reaching MRD negativity by multiparametric flow-cytometry [44•]. At the American Society of Hematology Annual Meeting 2013, preliminary results of a phase 2 study looking at effect of low dose bortezomib (a proteasome inhibitor) on bone formation in SM patients was presented [45]. In this study, the dose of bortezomib used was 0.7 mg/m2. Of the 13 evaluable patients, 6 patients (46 %) had an improvement in hip T score (mean T score improvement 0.41, range 0.1–1.35).

Dietary Supplements

Dietary supplements such as cucurmin, green tea extract, sea cucumber extract have been investigated in SMM. Golombick at al studied the effect of cucurmin vs. placebo in SMM in a RCT with crossover design. In this study, 17 SMM patients and 19 MGUS patients were enrolled and 25 patients completed the study. The results showed that cucurmin therapy decreased free light-chain ratio (rFLC), reduced the difference between clonal and non-clonal light-chain and involved free light-chain [46]. A phase 2 study by Verma et al. evaluated TBL12 sea cucumber extract in patients with SMM [47]. Fifteen patients were evaluable with a median follow-up of 21 months. The median duration of response noted was 21 months and five patients progressed while on treatment. This study terminated early due lack of funding. Another study investigating Polyphenon E, an oral capsule extracted from green tea in patients with MGUS and SMM closed early due to low accrual [48].

Ongoing Studies

Multiple research studies are underway in SMM investigating established MM drugs and novel agents (Table 1).

A phase 2 study (NCT02415413) with KRd induction plus high dose melphalan and autologous stem cell transplant followed by consolidation KRd and maintenance Rd in patients with SMM and age < 65 is currently recruiting participants [49]. This study is expected to complete in May 2017. This is the first study investigate the role of transplant in high-risk SMM and its results will guide the future direction of SMM treatment. Another study sponsored by the NCI (NCT01169337) investigating lenalidomide and dexamethasone compared to observation (similar design to Spanish study by Mateos et al.) is actively recruiting as well [50]. Once resulted, this study will provide further insights about the role of lenalidomide therapy in high-risk SMM.

The other novel agents with promising results MM are also being researched in SMM as well. A phase 2 trial of elotuzumab (a monoclonal antibody targeting signaling lymphocytic activation molecule F7) and lenalidomide with or without dexamethasone in high-risk smoldering myeloma is ongoing [51]. Another phase 2 trial investigating three

Table 1 Select ongoing trials in smoldering myeloma

Clinical trial no.	Phase	Drug/intervention	Study title	Expected completion
NCT01965834	2	Fenofibrate	Phase II study to evaluate fenofibrate therapy in patients with smoldering or symptomatic multiple myeloma	March 2017
NCT02316106	2	Daratumumab	A study to evaluate three dose schedules of daratumumab in participants with smoldering multiple myeloma	November 2017
NCT02415413	2	KRd induction, high dose melphalan with transplant, KRd consolidation and Rd maintenance.	Carfilzomib in treatment patients under 65 years with high-risk smoldering multiple myeloma	May 2017
NCT01169337	3	Lenalidomide	Lenalidomide or observation in treating patients with asymptomatic high-risk smoldering multiple myeloma	Jan 2026 (Final data collection for primary outcome).
NCT02492750	1/2	Lenalidomide, dexamethasone, and anakinra.	Lenalidomide and dexamethasone with or without anakinra in treating patients with early stage multiple myeloma	July 2020
NCT02279394	2	Elotuzumab	Trial of combination of elotuzumab and lenalidomide +/− dexamethasone in high-risk smoldering multiple myeloma	January 2020

different doses of daratumumab (a CD-38 antibody) is currently recruiting participants and expected to complete in 2017 [52].

Our Approach in the Clinic

In patients presenting with incidental paraproteinemia, we complete the initial work up to include lab tests, bone marrow biopsy, and prefer sensitive imaging studies like PET/CT or MRI to ensure no lesions are noted and establish appropriate risk stratification. If patients do not have any MDEs and have a low-risk for progression based on Mayo criteria, we follow them with labs and physical exam every 3–4 months for 2 years and then semi-annually thereafter. After 5 years, if there is no evolution of monoclonal gammopathy, then patients are followed annually. If patients have high-risk disease, they are considered for clinical trials exploring early intervention like the ECOG-E3A06 trial, studies evaluating immunotherapies or novel agents such as daratumumab in SMM patients (NCT02316106). Additional clinical trials exploring alternative treatment strategies in SMM are currently being developed. We obtain additional sequential imaging in high-risk patients with single focal bone marrow lesions or suspicious lesions of concern, especially if patients are noted to have bone marrow plasma cell percentage >35–40 %. High-risk patients are followed every 3 months to ensure they do not develop MDEs. In high-risk patients, we have a low threshold for more sensitive imaging like PET/CT or MRI based on complaints during follow-up.

Conclusion

The definition and understanding of SMM has evolved over the last decade. It is clear that multiple clinical and genetic risk factors interplay and alter the course of smoldering myeloma. A group of previously "very high-risk" SMM patients are now considered to have myeloma-defining events and treated as such. A subgroup of high-risk SMM patients is being defined, and early intervention with anti-myeloma therapy is the subject of research in this group. Incorporating newer molecular and imaging markers to existing risk prediction model will help in pinpointing the high-risk group that would benefit with treatment precisely. Outside of clinical trials, close surveillance remains the standard of care for this group. Finally we may also be able to define a "low-risk" group that has a rate of progression similar to MGUS and observation alone to detect the rare progression will suffice.

The focus of research in smoldering myeloma in the future will be towards ascertaining the right therapy and its optimal timing. The use of novel MM agents will percolate in to the realm of smoldering myeloma. Finding the therapy with maximal benefit and minimal adverse effect will be crucial. Predictive markers for treatment efficacy, utility of high dose chemotherapy with stem cell transplantation and maintenance therapy are key questions that will be answered in the next few years. Future research trials would tell us whether early treatment of high-risk SMM would yield us the evasive "cure".

In the future, we may be able to use imaging, genetic and other tools to be able to dichotomize smoldering myeloma patients into those that have a very high likelihood of progression and hence need treatment to try and alter the natural history of the disease and those that have a truly low likelihood of progression who can be managed with observation alone and will likely not progress to symptomatic myeloma in their lifetime.

Compliance with Ethical Standards

Conflict of Interest Srinath Sundararajan, Abhijeet Kumar, and Neha Korde each declare no potential conflicts of interest.

Amit Agarwal reports personal fees from Celegene, Novartis, Millenium, and Onyx.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (mgus) consistently precedes multiple myeloma: a prospective study. Blood. 2009;113(22):5412–7.
2. •• Dhodapkar MV, Sexton R, Waheed S, et al. Clinical, genomic, and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (swog s0120). Blood. 2014;123(1):78–85. **A very important prospective trial of patients with asymptomatic myeloma (MGUS or SMM) that identified a predictive gene expression profiling score (GEP-70) apart from conventional clinical and imaging predictors for progression**.
3. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med. 2007;356(25):2582–90.
4. Larsen JT, Kumar SK, Dispenzieri A, Kyle RA, Katzmann JA, Rajkumar SV. Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma. Leukemia. 2013;27(4):941–6.
5. Rajkumar SV, Gupta V, Fonseca R, et al. Impact of primary molecular cytogenetic abnormalities and risk of progression in smoldering multiple myeloma. Leukemia. 2013;27(8):1738–44.
6. Hillengass J, Weber MA, Kilk K, et al. Prognostic significance of whole-body mri in patients with monoclonal gammopathy of undetermined significance. Leukemia. 2014;28(1):174–8.

7. Merz M, Hielscher T, Wagner B, et al. Predictive value of longitudinal whole-body magnetic resonance imaging in patients with smoldering multiple myeloma. Leukemia. 2014;28(9):1902–8.
8. Zhao S, Choi M, Heuck C, et al. Serial exome analysis of disease progression in premalignant gammopathies. Leukemia. 2014;28(7):1548–52.
9. Kristinsson SY, Anderson WF, Landgren O. Improved long-term survival in multiple myeloma up to the age of 80 years. Leukemia. 2014;28(6):1346–8.
10. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase iii us intergroup trial s9321. J Clin Oncol. 2006;24(6):929–36.
11.•• Agarwal A, Ghobrial IM. 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. 2013;19(5):985–94. **Updated 2014 IMWG definitions for SMM, MGUS and MM. SMM with bone marrow plasma cell >60 % and involved:univolved light-chain ratio >100 were reclassied as MM**.
12. Kyle RA, Durie BG, Rajkumar SV, et al. 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. 2010;24(6):1121–7.
13. Rajkumar SV, Kyle RA, Buadi FK. Advances in the diagnosis, classification, risk stratification, and management of monoclonal gammopathy of undetermined significance: implications for recategorizing disease entities in the presence of evolving scientific evidence. Mayo Clin Proc. 2010;85(10):945–8.
14. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International myeloma working group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538–48.
15. Perez-Persona E, Vidriales MB, Mateo G, et al. 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. 2007;110(7):2586–92.
16. Dispenzieri A, Kyle RA, Katzmann JA, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. Blood. 2008;111(2):785–9.
17. Kastritis E, Terpos E, Moulopoulos L, et al. Extensive bone marrow infiltration and abnormal free light chain ratio identifies patients with asymptomatic myeloma at high risk for progression to symptomatic disease. Leukemia. 2013;27(4):947–53.
18. Rajkumar SV, Larson D, Kyle RA. Diagnosis of smoldering multiple myeloma. N Engl J Med. 2011;365(5):474–5.
19. Nowakowski GS, Witzig TE, Dingli D, et al. Circulating plasma cells detected by flow cytometry as a predictor of survival in 302 patients with newly diagnosed multiple myeloma. Blood. 2005;106(7):2276–9.
20. Kumar S, Rajkumar SV, Kyle RA, et al. Prognostic value of circulating plasma cells in monoclonal gammopathy of undetermined significance. J Clin Oncol. 2005;23(24):5668–74.
21. Pardanani A, Witzig TE, Schroeder G, et al. Circulating peripheral blood plasma cells as a prognostic indicator in patients with primary systemic amyloidosis. Blood. 2003;101(3):827–30.
22. Bianchi G, Kyle RA, Larson DR, et al. High levels of peripheral blood circulating plasma cells as a specific risk factor for progression of smoldering multiple myeloma. Leukemia. 2013;27(3):680–5.
23. Witzig TE, Kyle RA, O'fallon WM, Greipp PR. Detection of peripheral blood plasma cells as a predictor of disease course in patients with smouldering multiple myeloma. Br J Haematol. 1994;87(2):266–72.
24. Khan R, Dhodapkar M, Rosenthal A, et al. Four genes predict high risk of progression from smoldering to symptomatic multiple myeloma (swog s0120). Haematologica. 2015;100(9):1214–21.
25. Neben K, Jauch A, Hielscher T, et al. 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. 2013;31(34):4325–32.
26. Moulopoulos LA, Dimopoulos MA, Smith TL, et al. Prognostic significance of magnetic resonance imaging in patients with asymptomatic multiple myeloma. J Clin Oncol. 1995;13(1):251–6.
27.• Hillengass J, Fechtner K, Weber MA, et al. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. J Clin Oncol. 2010;28(9):1606–10. **A recent study showing the PET/CT scan's role in identifying high risk SMM patients**.
28. Dimopoulos MA, Hillengass J, Usmani S, et al. Role of magnetic resonance imaging in the management of patients with multiple myeloma: a consensus statement. J Clin Oncol. 2015;33(6):657–64.
29. Siontis B, Kumar S, Dispenzieri A, et al. Positron emission tomography-computed tomography in the diagnostic evaluation of smoldering multiple myeloma: identification of patients needing therapy. Blood Cancer J. 2015;5, e364.
30. Zamagni E, Nanni C, Gay F, et al. 18f-fdg pet/ct focal, but not osteolytic, lesions predict the progression of smoldering myeloma to active disease. Leukemia. 2015.
31. Kazandjian D, Mailankody S, Korde N, Landgren O. Smoldering multiple myeloma: pathophysiologic insights, novel diagnostics, clinical risk models, and treatment strategies. Clin Adv Hematol Oncol. 2014;12(9):578–87.
32. Rajkumar SV, Landgren O, Mateos MV. Smoldering multiple myeloma. Blood. 2015;125(20):3069–75.
33. Anderson KC. Multiple myeloma: new uses for available agents, excitement for the future. J Natl Compr Canc Netw. 2015;13(5 Suppl):694–6.
34. Anderson KC, Alsina M, Bensinger W, et al. Multiple myeloma, version 1.2013. J Natl Compr Canc Netw. 2013;11(1):11–7.
35. Hjorth M, Hellquist L, Holmberg E, Magnusson B, Rodjer S, Westin J. Initial versus deferred melphalan-prednisone therapy for asymptomatic multiple myeloma stage I—a randomized study. Myeloma group of western Sweden. Eur J Haematol. 1993;50(2):95–102.
36. Riccardi A, Mora O, Tinelli C, et al. 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. 2000;82(7):1254–60.
37. Alexanian R, Barlogie B, Dixon D. Prognosis of asymptomatic multiple myeloma. Arch Intern Med. 1988;148(9):1963–5.
38. Detweiler-Short K, Hayman S, Gertz MA, et al. Long-term results of single-agent thalidomide as initial therapy for asymptomatic (smoldering or indolent) myeloma. Am J Hematol. 2010;85(10):737–40.
39. D'arena G, Gobbi PG, Broglia C, et al. Pamidronate versus observation in asymptomatic myeloma: final results with long-term follow-up of a randomized study. Leuk Lymphoma. 2011;52(5):771–5.
40. Musto P, Petrucci MT, Bringhen S, et al. A multicenter, randomized clinical trial comparing zoledronic acid versus observation in patients with asymptomatic myeloma. Cancer. 2008;113(7):1588–95.
41. Barlogie B, Van Rhee F, Shaughnessy Jr JD, et al. Seven-year median time to progression with thalidomide for smoldering myeloma: partial response identifies subset requiring earlier salvage therapy for symptomatic disease. Blood. 2008;112(8):3122–5.
42. Witzig TE, Laumann KM, Lacy MQ, et al. A phase III randomized trial of thalidomide plus zoledronic acid versus zoledronic acid alone in patients with asymptomatic multiple myeloma. Leukemia. 2013;27(1):220–5.

43.•• Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med. 2013;369(5):438–47. **Only study so far to show overall survival advantage with treatment in patients with high-risk SMM**.

44.• Korde N, Roschewski M, Zingone A, et al. Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. JAMA Oncol. 2015;1(6):746–54. **A recent study showing the efficacy if carfilzomib based triplet therapy in a small subset of SMM patients with >90 % achieving MRD negativity**.

45. Zangari MBTSM. Effect of low dose bortezomib on bone formation in smoldering myeloma patients. Am Soc Hematol. 2013.

46. Golombick T, Diamond TH, Manoharan A, Ramakrishna R. Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and curcumin: a randomized, double-blind placebo-controlled cross-over 4g study and an open-label 8g extension study. Am J Hematol. 2012;87(5): 455–60.

47. Desai A LM, Marcus S. A phase II trial of tbl12 sea cucumber extract in patients with untreated asymptomatic myeloma. Blood. 2014;124(21).

48. Myeloma GTEITPWMGOUSaOSM. Green tea extract in treating patients with monoclonal gammopathy of undetermined significance and/or smoldering multiple myeloma.

49. Nct02415413. Carfilzomib in treatment patients under 65 years with high risk smoldering multiple myeloma.

50. Nct01169337. Lenalidomide or observation in treating patients with asymptomatic high-risk smoldering multiple myeloma.

51. Nct02279394. Trial of combination of elotuzumab and lenalidomide +/− dexamethasone in high-risk smoldering multiple myeloma.

52. Nct02316106. A study to evaluate 3 dose schedules of daratumumab in participants with smoldering multiple myeloma.