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Development of Early Treatment Strategies for High-Risk Myeloma Precursor Disease in the Future

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Abstract

Smoldering myeloma (SMM) is a precursor state of multiple myeloma. It is defined by an M-protein concentration ≥ 3 g/dL and/or $\geq 10\%$ clonal bone marrow plasma cells, in the absence of end-organ damage. Based on clinical observations, the natural history of SMM varies greatly, from stable, monoclonal gammopathy of undetermined significance (MGUS)-like disease to highly progressive disease. Using conventional clinical markers, SMM patients can be stratified into clinical risk groups. However, due to considerable molecular heterogeneity, we currently lack reliable markers to predict prognosis for individual SMM patients. Based on the International Myeloma Working Group 2010 guidelines, patients diagnosed with MGUS and SMM should not be treated outside of clinical trials. Overall, treatment trials for MGUS patients are complicated, as these individuals are relatively healthy and the majority has a low life-time risk of progression, especially when other causes of death are taken into account. In contrast to MGUS, early treatment strategies for SMM are particularly attractive, as the rate of progression to multiple myeloma is substantially higher. Until recently, potent drugs with reasonable toxicity profiles have not been available for the development of early multiple myeloma treatment strategies. This review discusses how the integration of novel biological markers and clinical monitoring of SMM could facilitate the development of early treatment strategies for high-risk SMM patients in the future.

Smoldering multiple myeloma (SMM) is an asymptomatic precursor state to multiple myeloma. About 3,000 to 5,000 cases are diagnosed annually in the United States, although estimates of prevalence are not reliable due to prior inconsistent diagnostic criteria and underdiagnosis from its asymptomatic nature.¹ Based on retrospective data from the Mayo Clinic, SMM has a 10% average annual risk of progression to multiple myeloma for the first 5 years following diagnosis, decreasing to 3% annually for the following 5 years, and becoming the same 1% annual rate of progression as monoclonal gammopathy of undetermined significance (MGUS) thereafter.²

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Based on the International Myeloma Working Group 2010 guidelines, patients diagnosed with MGUS and SMM should not be treated outside of clinical trials.³ This view is a reflection of the fact that prior studies have found no significant benefits of treatment initiation in myeloma precursor disease.^{4,5} However, these prior studies were conducted in the era of melphalan-based therapies. Indeed, until recently, potent drugs with reasonable toxicity profiles have not been available for the development of early multiple myeloma treatment strategies. This review discusses how the integration of novel biological markers and clinical monitoring of SMM could facilitate the development of early treatment strategies for high-risk SMM patients in the future. We also discuss future directions and shed light on gaps in the literature.

PATHOGENESIS AND PROGNOSIS

Largely due to the striking heterogeneity of their molecular profiles, the pathogenesis of MGUS, SMM, and multiple myeloma remains poorly understood. Clinically, SMM is a heterogeneous disorder consisting of disease with (1) stable, MGUS-like features; (2) an abrupt course to multiple myeloma; and (3) an intermediate, slowly progressive course. From a molecular perspective, gene-expression profiling (GEP) studies have revealed at least seven subtypes of multiple myeloma,⁶ but a prospective study to correlate GEP and other biomarkers to clinical course in MGUS and SMM has not yet been performed. While translational studies have made great strides towards generating new molecular descriptions of these disease entities and their transitions, they are still largely overlapping and sampling bias may exist in small translational studies, necessitating validation with large prospective studies to develop molecular predictors for which patients will endure which clinical course.

The first and largest systematic study focusing on SMM was based on retrospective data from 276 patients with SMM seen at the Mayo Clinic in the 1970–1995 period.² In this study, the heterogeneity of SMM was formalized through a subgroup analysis of patients stratified into three groups: *group 1* 10% bone marrow plasma cells and ≤ 3 g/dL of M-protein; *group 2* 10% bone marrow plasma cells and ≤ 3 g/dL of M-protein; and *group 3* 10% bone marrow plasma cells and ≤ 3 g/dL of M-protein. Patients in group 1 had a cumulative 15-year risk of progression of 87% with a median time-to-progression (TTP) of 2 years, patients in group 2 had 70% progression at 15 years with a median TTP of 8 years, and patients in group 3 had a cumulative risk of progression of 39% at 15 years with a median TTP of 19 years. It follows from the increased production of M-protein that there would be a reduction in uninvolved immunoglobulins, which was found to be an independent risk factor. Last, it was found that patients with an IgA heavy chain on average progressed faster than those with an IgG heavy chain.² Analysis of serum samples from 273 of the 276 patients from the above study with a free light-chain (FLC) assay later found an increase in the risk of progression to MM when the kappa/lambda FLC ratio deviated outside the reference range of 0.125 to 8 defined in the study. This factor was used to refine the previous risk stratification scheme, with the highest risk group three times more likely to progress at 5 years than the lowest risk group.⁷

Immunophenotyping with multi-parameter flow cytometry is an attractive technique for determining prognosis in SMM by identifying high levels of neoplastic plasma cells

compared to normal ones, which is likely in patients whose disease has more malignant potential. In a study conducted by the Spanish PETHEMA study group, Perez-Persona and colleagues immunophenotyped bone marrow aspirates of 93 patients with SMM.⁸ They found that in patients for whom these markers indicated 95% aberrant plasma cells (aPC), the relative risk of progression at 5 years was 8.5 in patients with MGUS and 5.4 in patients with SMM. This study also found that reduction in at least one uninvolved immunoglobulin was an independent risk factor for progression of SMM.⁸ A risk stratification scheme generated from these data shows that the risks of progression for patients with neither, one, or both risk factors at 5 years were 4%, 46%, and 72%, respectively ($P < .001$).⁸ A recent study by the same group found that 95% aPC could differentiate risk within the subgroups of evolving SMM or MGUS, defined by a >10% increase in M-protein 1 and 3 years from diagnosis, respectively. However, evolving SMM subtype was not found to be significant in a multivariate analysis of progression-free survival.^{9,10} Integrating other markers into such a risk stratification scheme will be important to determine which patients will ultimately progress.

DEVELOPMENT OF EARLY TREATMENT STRATEGIES

Among the first studies examining treatment of SMM was a 1988 retrospective study of 23 patients with SMM and 10 patients with lytic lesions but no symptoms. These patients were treated with one of two chemotherapy regimens, but the study failed to show a statistically significant difference in the endpoints of remission or survival.⁴ As this study was limited in its size and design, a randomized controlled trial of initial (at diagnosis) versus delayed (at symptoms) treatment with melphalan–prednisone for 50 patients with SMM or indolent multiple myeloma (IMM; asymptomatic disease but with evidence of end-organ damage) was performed, finding no difference in response rate, response duration, or survival.⁵ Based on these observations, for several years it has been deemed inappropriate to recommend patients undergo a difficult chemotherapy regimen with no evidence of a clinical benefit. However, both of these studies were performed when the best available treatment for multiple myeloma was melphalan–prednisone, a regimen with a poor therapeutic index for treatment of an asymptomatic condition.

The development of novel agents with improved efficacy and less toxicity have renewed interest in the treatment of SMM. Thalidomide is a non-cytotoxic drug used to treat refractory multiple myeloma that has been shown to have anti-inflammatory, anti-angiogenic, and immunomodulatory properties.^{11,12} In 2001, a trial of thalidomide as treatment for SMM in 16 patients was performed. Partial response (PR) was achieved in 38% of patients.¹³ These data may be confounded by the inclusion of patients with IMM who would now be classified as having multiple myeloma. In 2008, a single-arm, phase II trial including 76 patients with SMM treated with thalidomide and pamidronate did not show a clear overall benefit to treatment. Paradoxically, patients who initially displayed at least a PR to thalidomide had a shorter median time to treatment (<2 years) than patients who showed no improvement (not reached in 8 years).¹⁴ Although it remains to be proven, the investigators speculate that this may be due to a greater initial response in patients with more proliferative tumors or selection of aggressive clones due to treatment. This study was

further complicated by poor tolerance to thalidomide, due to peripheral neuropathy and dizziness resulting in discontinuation in more than half of the patients.¹⁴

These dose-limiting toxicities have prompted the use of less toxic drugs that share mechanistic features with thalidomide.¹² Lenalidomide is a second-generation immunomodulatory drug that has proven efficacy used with dexamethasone in both relapsed-refractory and newly diagnosed multiple myeloma.^{12,15–19} While the side effect profile was improved relative to thalidomide, bone marrow suppression and venous thromboembolism remained as significant adverse events.^{16,20} The first phase III clinical trial using novel drugs (lenalidomide–dexamethasone *v* clinical surveillance) in SMM is currently ongoing in Spain.²¹ Preliminary results were first presented at the 2009 meeting of the American Society of Hematology. In the surveillance arm, 50% of patients with high-risk SMM progressed to active multiple myeloma in 19 months. However, in 45 patients who began and continued active treatment with lenalidomide–dexamethasone, no disease progression was observed after a median follow-up of 16 months.²² Importantly, at this time, we do not know whether SMM patients treated with lenalidomide–dexamethasone will have a longer overall survival than those in the surveillance arm. Also, we do not know if there will be differences between the two study arms with regard to quality of life. Lastly, we do not know whether patients in the lenalidomide–dexamethasone treatment arm who later will develop multiple myeloma may have an altered susceptibility to therapy. These are very important questions that need to be addressed as soon as follow-up data are mature and allow formal, sufficiently powered statistical analysis.

During the winter of 2010/2011, a few new SMM treatment studies have opened in the United States. For example, the Eastern Cooperative Oncology Group (ECOG) and the Southwest Oncology Group (SWOG) in North America have initiated a collaborative, randomized phase III study designed to compare lenalidomide alone (*v* clinical surveillance) in SMM patients.²³ Furthermore, at the National Cancer Institute (NCI), at the National Institutes of Health (NIH), in Bethesda, MD, a novel phase II study for SMM recently opened.²⁴ This study features administration of IPH2101, a monoclonal anti-KIR antibody that blocks inhibitory KIR receptors on the patient's own natural killer (NK) cells, thereby augmenting NK cell-mediated killing of myeloma cells²⁴ (Table 1).

Lastly, a few smaller trials have studied other interventions with benign side effect profiles aimed at limiting the progression of SMM or MGUS, including anakinra, a targeted interleukin-1 receptor antagonist²⁵; curcumin, a traditional Indian Spice with preclinical anti-myeloma activity^{26–29}; and bisphosphonates, believed to block the initial formation of lytic lesions and alter the marrow microenvironment.^{30,31} For example, in 2008, a randomized study compared zoledronic acid versus surveillance in SMM and demonstrated reduced skeletal events in the treatment arm (zoledronic 55.5% *v* surveillance 78.3%; $P = .041$); however, there was no difference in median TTP ($P = .83$) to full-blown multiple myeloma.³⁰ Taken together, at this time, none of these studies have had sufficient power or study design to significantly alter clinical practice. Some data are further limited by use of nonstandard endpoints and response criteria.³² Despite these limitations, these trials are crucial in their ability to open avenues for further research. Selected published and ongoing clinical trials studying treatment of SMM are listed and described in Table 1.

SUMMARY AND FUTURE DIRECTIONS

As stated earlier, based on the International Myeloma Working Group 2010 guidelines, patients diagnosed with MGUS and SMM should not be treated outside of clinical trials.³ In standard clinical practice, SMM patients shall receive close follow-up with repeat laboratory testing at 2 to 3 months during the first year and, if stable, every 4 to 6 months thereafter due to the high initial risk of progression.³

Overall, treatment trials for MGUS patients are complicated, as these individuals are relatively healthy and the majority have a low life-time risk of progression, especially when other causes of death are taken into account.³³ Consequently, it seems reasonable to propose that an ideal treatment would be very effective, nontoxic, and directed towards patients with high risk of progression. At this time, we do not have access to any such drugs.

The high rate of progression of SMM into symptomatic disease makes the idea of an early treatment strategy appealing to clinicians, though as of yet no particular treatment regimen has demonstrated a clear benefit for these patients in terms of overall survival. Several promising clinical trials are already in progress both in Europe and in the United States (see Table 1). The first studies using novel drugs in SMM were based on thalidomide.^{13,14} Using a second-generation immunomodulatory drug, lenalidomide, in combination with dexamethasone, the Spanish study group initiated the first randomized SMM trial.²² This study was followed by a lenalidomide-based study (without dexamethasone) launched in 2010 by the ECOG/SWOG study groups in the United States. Furthermore, a novel phase II study based on a monoclonal anti-KIR antibody that augments NK cell-mediated killing of myeloma cells opened in 2010 at the NCI/NIH (Table 1).

In the future, novel agents currently used to treat relapsed or refractory multiple myeloma may be applied in clinical trials designed for SMM patients. For example, pomalidomide, a third-generation immunomodulatory drug, has been found to be efficacious in patients with relapsed multiple myeloma with less bone marrow suppression than Lenalidomide.³⁴ Bortezomib, an inhibitor of the 26S proteasomal subunit, has been used successfully to treat both newly diagnosed and relapsed multiple myeloma, though peripheral neuropathy and bone marrow suppression remain clinical challenges.^{35,36} Carfilzomib, a second-generation proteasome inhibitor, has shown promise in two phase I and one phase II trial for the treatment of multiple myeloma with potentially fewer side effects than bortezomib,³⁷ although the frequent, intravenous administration of these drugs is not optimal for treatment of SMM. These newer drugs with more favorable side effect profiles may have the potential to be used in the treatment of SMM without the frequent treatment-terminating adverse effects of thalidomide. Also, several other small molecules and monoclonal antibodies have shown promise in preclinical and early clinical studies.³⁸ The time may be right for the commencement of clinical trials of these novel agents in the treatment of SMM, though care should be taken that such studies analyze key endpoints such as time to progression and overall survival, as past experience has indicated that partial and complete responses may not be illustrative of benefit.

As research moves forward in characterizing precursor disease, it is important to tread carefully in clinical trials involving treatment of an asymptomatic disease state. Although it remains to be proven, we have recently speculated on potential scenarios that could result from early treatment of SMM (Figure 1).³⁹ The first scenario—what we would call the “dream scenario”—suggests early treatment may facilitate cure. The second scenario—in our opinion, a more realistic scenario in the present era of available drugs—envision myeloma disease similar to any chronic disease state where therapy is needed to maintain disease control. Thus, in the second scenario, multiple myeloma is being approached and treated like, for example, hypertension. Finally, theoretically, one might speculate that early treatment could lead to a paradoxical decrease in survival or time to progression due to selection of aggressive clones that are more capable of competing in the treatment-altered microenvironment.⁴⁰ Since we do not know if this scenario is likely to occur, should future trials indicate that multiple myeloma developing after early treatment is more aggressive, this question should be addressed. Because none of these scenarios has been proven true, it is very important to conduct well-designed correlative studies in clinical trials aimed to treat SMM patients.

In summary, while current evidence does not support the treatment of SMM outside of clinical studies, it does in our opinion support the development of early treatment trials that integrate molecular monitoring. Future goals should be (1) to provide molecularly based predictions of transformation from MGUS/SMM to multiple myeloma; (2) to use molecular markers to counsel patients with regard to future clinical follow-up/intervention; and (3) to develop novel treatments for patients with high-risk multiple myeloma precursor disease, aiming to delay progression and potentially offer cure.

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Figure 1.

Three possible scenarios resulting from treatment of smoldering myeloma. Progression of untreated high risk SMM to full blown myeloma is shown on the left. SMM patients with two or three risk factors (see Pathogenesis and Prognosis) have a median TTP of 5 and 2 years, respectively. Scenarios no. 1–3 illustrate possible outcomes from early treatment of SMM. No. 1 (center left) represents a complete cure of MM, which has not yet been reliably achieved by any current treatment modalities. This would likely require more intense treatment, necessitating improved risk stratification of patients. Ultimately, targeted therapies may be able to achieve cure. No. 2 (center right) represents the generation of a chronic, asymptomatic disease state requiring ongoing maintenance therapy. This is a likely outcome of using immunomodulatory and targeted agents available in the near future. No. 3 (right) illustrates the theoretical possibility of the selection of a particularly aggressive, resistant clone. While time to progression is extended in this scenario, overall survival may not be improved, as symptomatic disease might progress unchecked if available treatments become less effective following early treatment. Future studies are needed to fully explore these possibilities. Taken together, we do not know which, if any, of these scenarios are true. Therefore, clinical trials aimed at developing treatments for SMM should incorporate well designed correlative studies to examine the biology of treatment response. Reproduced from Waxman et al, 2010, with permission.³⁹

Table 1.
Selected Clinical Studies of Strategies to Prevent Progression of MGUS, SMM, and Early-Stage Multiple Myeloma

Reference	Study Design	Intervention	No. of Patients	Outcome/Comment
Alexanian, 1988 ⁴	Retrospective cohort study	VAD or MP	23SMM, 10IMM	Because the treatment of MM remains palliative, chemotherapy should be withheld until symptoms
Hjorth, 1993 ⁵	Randomized-controlled trial	Initial v deferred MP therapy	50 SMM and IMM (25/25)	Similar response rate, response duration, and survival
Rajkumar, 2001 ¹³	Single-arm pilot study	Thalidomide	16 SMM and IMM	MR or better in 11/16. Microvessel density did not predict response.
Musto, 2008 ³⁰	Open-label randomized controlled trial	Zoledronate	163 SMM (81/82)	Zoledronate for 1 year decreased risk of skeletal-related disease, but TTP was similar (P = .83)
Barlogie, 2008 ¹⁴	Single-arm, phase II trial	Thalidomide/pamidronate	76 SMM	Median TTP 7 years; PR identifies subset requiring earlier salvage therapy for symptomatic disease
Lust, 2009 ²⁵	Single-arm, phase II trial	Anakinra (IL-1 receptor antagonist)	47 SMM and IMM (25 received anakinra and DEX)	Median PFS was 37.5 mo. MR (n = 3), PR (n = 5). 8 patients stable on drug for 4 years.
Golombick, 2009 ²⁶	Single-blind, randomized, cross-over pilot study	Curcumin v placebo	26 MGUS	5 of 10 patients with M-protein >2 g/dL had decreased M-protein (12–30% reduction)
Kalaycio, 2004 (ongoing) ⁴¹	Double-blind, randomized controlled trial	Celoxicib v placebo	36 MGUS and SMM	Aim: to test if celoxicib reduces the M-protein concentration
Mateos, 2007 (ongoing) ²¹	Open-label randomized controlled trial	Lenalidomide + DEX v observation	120 SMM	Aim: to evaluate if lenalidomide + DEX extend TTP
Ballester, 2009 (ongoing) ⁴²	Unblinded, nonrandomized trial	Omega-3 fatty acids	48* MGUS, SMM, or CLL	Aim: to assess if Omega-3 fatty acids reduce activated NF-κB levels in peripheral blood lymphocytes
Zonder, 2009 (ongoing) ⁴³	Single-arm pilot study	Green tea extract	17* MGUS or SMM	Aim: to test if green tea extract reduces the M-protein concentration
Lonia, 2010 (ongoing) ²³	Open-label randomized controlled trial	Lenalidomide v observation	370* SMM	Aim: to evaluate if lenalidomide extends TTP
Landgren, 2010 (ongoing) ²⁴	Single-arm phase II trial	Anti-KIR monoclonal antibody	21 SMM	Aim: to evaluate if anti-KIR reduces the M-protein concentration 50% from baseline

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; CLL, chronic lymphocytic leukemia; IMM, indolent multiple myeloma (asymptomatic but with evidence of end-organ damage); MR, minor response (25%–50% decrease in M-protein); PR, partial response (>50% decrease in M-protein); CR, complete response (no detectable M-protein); MP, melphalan/prednisone; VAD, vincristine, doxorubicin, dexamethasone; DEX, dexamethasone; IL-1, interleukin-1; TTP, time to progression; PFS, progression-free survival.

* Estimated enrollment.

Adapted from Waxman et al, 2010, with permission.³⁹