Smoldering (Asymptomatic) Multiple Myeloma: Current Diagnostic Criteria, New Predictors of Outcome, and Follow-Up Recommendations

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A B S T R A C T

Purpose

To provide an overview on smoldering (asymptomatic) multiple myeloma (SMM) including current diagnostic criteria, predictors of progression, pattern of progression, and outcome.

Design

A comprehensive review of the literature on risk factors for progression, treatment attempts to delay progression and outcome in patients with SMM.

Results

The risk factors for progression of SMM include: plasma cell mass including M-protein size and percentage of bone marrow clonal plasma cells (BMPC), abnormal free light chain ratio, proportion of phenotypically abnormal BMPC, immunoparesis, evolution pattern (evolving v nonevolving), and pattern of magnetic resonance imaging abnormalities. Most patients with SMM progress with anemia and/or skeletal involvement. Immediate therapy with cytotoxic agents, such as melphalan/prednisone has not resulted in improved outcome. Patients should not be treated until progressive disease with end-organ damage occurs. Increasing anemia is the most reliable indicator of progression.

Conclusion

These recently recognized predictors of outcome may be helpful for better disease monitoring and for investigation of new treatment approaches. Thus, recommendations for follow-up every to 3 to 6 months depending on the risk of progression are suggested, and clinical trials with new noncytotoxic biologically derived agents to delay progression, particularly in high-risk patients, are ongoing.

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INTRODUCTION

In 1980, Kyle and Greipp¹ first described smoldering multiple myeloma (SMM) as a distinct clinical entity characterized by the presence of a serum M-protein value higher than 3 g/dL, bone marrow clonal plasma cells (BMPC) involvement of 10% or higher, and no bone lytic lesions or clinical manifestations attributable to the monoclonal plasma-cell proliferative disorder. The original cohort of patients described by Kyle and Greipp¹ remained stable with no need for chemotherapy for longer than 5 years. In the same year, Alexanian² reported 20 patients with the so-called indolent myeloma who were asymptomatic, had a hemoglobin (Hb) level higher than 10 g/dL, and had no more than three lytic bone lesions. These patients also did not require chemotherapy for a median of 3 years from diagnosis.² Since these seminal observations, several series of patients with asymptomatic disease and

classified either as SMM, indolent myeloma, asymptomatic myeloma, or low tumor mass myeloma have been reported.³⁻⁹ However, the diagnostic criteria have not been uniform, thus resulting in important differences in time to progression and in a lack of consistent predictors of outcome between the different series. In 2003, the International Myeloma Working Group (IMWG) agreed on a new definition of SMM consisting of a serum M-protein of ≥ 3 g/dL and/or $\geq 10\%$ bone marrow plasma cells with no evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia or bone lesions [CRAB]).¹⁰ The Mayo Group has refined these criteria to clarify that the M protein must be of immunoglobulin (Ig) G or IgA subtype and that the plasma cells need to be clonal.¹¹ In addition, new predictors of progression have been recently recognized.¹²⁻¹⁴ The goal of this review is to provide a comprehensive overview of SMM as currently defined, including diagnosis, predictors of

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Table 1. Diagnostic Criteria of Smoldering Multiple Myeloma in the Different Reported Series

Study	M Protein (g/dL)	Bone Marrow Plasma Cells (%)
Kyle and Greipp, 1980 ¹	≥ 3	≥ 10
Alexanian et al 1988 ³	> 2	—
Wisloff et al 1991 ⁴	IgA > 1.5; IgG > 3	—
Facon et al 1995 ⁶	—	> 15
Weber et al 1997 ⁷	> 2.5	—
Cesana et al 2002 ^{8*}	IgA 2.1-4.9; IgG 3.6-6.9; light chain proteinuria > 1 g/24 h	> 10
Rosiñol et al 2003 ^{9†}	≥ 3	≥ 10
IMWG 2003 ^{10‡}	≥ 3	≥ 10

Abbreviations: Ig, immunoglobulin; IMWG, International Myeloma Working Group.

*Either diagnostic criterion is acceptable.

†Both diagnostic criteria are required.

‡Either or both diagnostic criteria are acceptable.

progression, pattern of progression, and overall outcome. We also provide follow-up and management recommendations for patients with SMM.

DIAGNOSTIC CRITERIA AND INCIDENCE

The different diagnostic criteria which have been used to define SMM are summarized in Table 1.^{1,3,4,6-10} In some studies only the M-protein size was taken into account^{3-5,7} while in the study by Facon et al⁶ the only criterion was a proportion of BMPC higher than 15%. In the study by Cesana et al,⁸ both the M protein amount and the proportion of BMPC were considered. This variability in the diagnostic criteria of SMM has resulted in important differences in clinical outcome among the reported series.³⁻⁹ In this context, the IMWG agreed on consensus criteria to define SMM based on an M-protein of 3 g/dL or greater and/or a proportion of BMPC of 10% or higher with no symptoms or complications resulting from the monoclonal gammopathy.¹⁰ These criteria have so far been only applied to two series.^{12,14}

The median age of the patients at diagnosis ranges from 65 to 70 years and the incidence of SMM varies from series to series although it usually is between 10% and 15% of all patients with MM.^{9,12,14}

DIFFERENTIAL DIAGNOSIS

SMM has to be distinguished from monoclonal gammopathy of undetermined significance (MGUS), symptomatic MM, and primary systemic amyloidosis (AL) (Table 2). Patients with MGUS have an M-protein concentration of less than 3 g/dL with no substantial amount of light chain in the urine, less than 10% BMPC plus the absence of skeletal involvement, anemia, hypercalcemia, or renal insufficiency that can be attributed the clonal plasma-cell proliferative disorder.^{15,16} When the M-protein size and the proportion of bone marrow plasma cells are consistent with MGUS but there is substantial albuminuria, congestive heart failure, renal failure, peripheral neuropathy, orthostatic hypotension, carpal tunnel syndrome, massive hepatomegaly, malabsorption syndrome, or any combination of the above, the most likely diagnosis is primary systemic amyloidosis (AL)

Table 2. Differential Diagnosis for MGUS, SMM, and Symptomatic MM

Feature	MGUS	SMM	Multiple Myeloma
BMPC, %	< 10 and	≥ 10 and/or	≥ 10 and/or
Serum monoclonal protein, g/L	< 3	≥ 3	≥ 3
Clinical manifestation	Absent	Absent	Present*

NOTE. From the International Myeloma Working Group.

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering (asymptomatic) multiple myeloma; MM, multiple myeloma; BMPC, bone marrow clonal plasma cells.

*Clinical features may include increased serum calcium concentrations, renal failure, anemia, skeletal involvement (lytic lesions), recurrent bacterial infections and/or extramedullary plasmacytomas.

resulting from the deposition of amyloidogenic light chains in organs and tissues. Patients with a serum M-protein ≥ 3 g/dL and/or a proportion of BMPC ≥ 10% with skeletal involvement (or soft tissue plasmacytomas), anemia, renal insufficiency, hypercalcemia, recurrent bacterial infections attributable to a plasma-cell proliferative disorder have symptomatic myeloma (Table 2).

Since the distinction between MGUS/SMM and MM depends on the end-organ damage that can be attributed to the plasma cell disorder, certain caveats must be kept in mind. Many elderly patients have concomitant diseases that can result in findings that mimic MM. Thus, some laboratory abnormalities and clinical features may occasionally be due to unrelated disorders. Some such situations include: mild increase in serum creatinine with or without nonselective proteinuria, due to diabetes or hypertension; anemia due to iron, vitamin B12, or folic acid deficiency, anemia of chronic disease if the patient has a chronic inflammatory or autoimmune disorder, or anemia due to myelodysplastic syndrome; as diffuse osteoporosis which is more frequent in the elderly, and particularly in women: a long lasting history of progressive osteoporosis with or without compression fractures is against the diagnosis of symptomatic MM, while a sudden onset often indicates active disease; coincidental hyperparathyroidism should be considered in a patient who presents with hypercalcemia, especially when lytic bone lesions are absent. The diagnostic clue may be a mild to moderate but stable hypercalcemia and serum parathyroid hormone measurements can confirm the suspected diagnosis. Finally, in patients with a single asymptomatic lytic bone lesion, the possibility of an associated benign bone cyst or a bone angioma should be considered, and a computed tomography scan or magnetic resonance imaging (MRI) may be helpful in the differential diagnosis.

RISK FACTORS FOR PROGRESSION

Series Published Before the IMWG Consensus Criteria

The large majority of patients with SMM will evolve into symptomatic MM and require treatment. The median time to progression (TTP) has ranged between 2 and 3 years.³⁻⁸ Since the recognition of SMM, a number of studies on possible predictors of progression to symptomatic MM have been reported.³⁻⁹ The risk factors for progression identified in older studies are presented in Table 3. The plasma cell mass measured by the size of the serum M-protein and/or the proportion of BMPCs has been a consistent risk factor for progression in most series.³⁻⁸ Other features with independent adverse impact on

Table 3. Factors Associated With Progression to Symptomatic MM and Risk Groups

Study by	Risk Factors	Risk Group by Factors		
		Low	Intermediate	High
Alexanian et al, 1988 ³	Lytic bone lesions; M protein > 30 g/L	0	—	1-2
Wisloff et al, 1991 ⁴	Lytic bone lesions; BMPC > 20%	0	—	1-2
Dimopoulos et al, 1993 ⁵	Lytic bone lesions; M protein > 30 g/L; proteinuria > 50 mg/24 h	No lysis, +0	No lysis, +1	Lysis, +2
Facon et al, 1995 ⁶	Hb < 12 g/L; BMPC > 20%; M protein > 30 g/L (IgG); M protein > 25 g/L (IgA)	0	1	2-3
Weber et al, 1997 ⁷	M protein > 30 g/L; IgA M-protein type; proteinuria > 50 mg/24 h	0	1	2-3
Cesana et al, 2002 ⁸	BMPC > 10%; IgA M-protein type; proteinuria	0	—	1-3

Abbreviations: MM, multiple myeloma; BMPC, bone marrow plasma cells; Hb, hemoglobin; Ig, immunoglobulin.

the risk of progression were the presence of light chain proteinuria (> 50 mg/24 hours^{4,6}) and an IgA monoclonal heavy chain.^{7,8} Some of these studies included patients with asymptomatic lytic bone lesions.³⁻⁵ When this was the case, the presence of lytic lesions implied a particularly poor prognosis with a median TTP of less than 1 year. For this reason, most authors have excluded these patients from their series of SMM.^{6-9,12} In fact, the presence of lytic bone lesions is not accepted in the current consensus criteria by the IMWG.¹⁰ The combination of the above mentioned prognostic factors has resulted in the identification of risk groups with different TTP. The median TTP in the low risk-group ranged from 3 to 8 years while high-risk patients usually evolved into symptomatic MM within the first 1 to 2 years after diagnosis.³⁻⁸

The prognostic impact of magnetic resonance imaging in patients with SMM has been investigated.¹⁷⁻²⁰ Between 30% and 50% of patients with SMM have an abnormal MRI and the presence of MRI abnormalities is a predictor of an earlier progression. In this regard, patients with an abnormal MRI have a median TTP of less than 1 year, while in those with no MRI abnormalities the median TTP is longer than 3 years.²⁰ In addition, the spinal MRI in patients with SMM may show three different patterns: focal, variegated, and diffuse.¹⁷ The abnormal signal intensity results from an increase in the bone marrow cellularity, and it is assumed that focal cell aggregates result in focal lesions, whereas a more extensive plasma cell involvement results in a diffuse pattern. It is also thought that the variegated pattern is due to plasma cell clusters dispersed on a background of otherwise normal bone marrow. The MRI pattern is of prognostic value. Thus, the focal pattern is associated with a shorter TTP when compared with the diffuse or variegated pattern (median, 6 v 16 v 22 months, respectively).¹⁷ Furthermore, the focal pattern is associated with a higher probability of compression fractures, such findings can be reasonably considered to be equivalent to the presence of early lytic bone disease.

The labeling index of BMPC is a measure of proliferative activity in monoclonal gammopathies and, if available, a helpful parameter in distinguishing SMM from symptomatic MM.²¹ The presence of abnormal peripheral blood monoclonal plasma cells, defined by an increase in either number or proliferative rate labeling index by slide-based immunofluorescent assays, was significantly correlated with TTP in a Mayo Clinic study.²² However, a shortcoming of this test is that it is not widely available in clinical practice.

Series Defined Using Uniform Criteria by the IMWG

Size of M protein and extent of marrow involvement. Kyle et al¹² reported the long-term outcome in a series of 276 patients diagnosed with SMM according to the new IMWG consensus criteria (ie, M-protein $\geq$ 3 g/dL and/or $\geq$ 10% BMPC). The actuarial probability of progression to MM or AL was 54% at 5 years, 66% at 10 years, and 73% at 15 years of follow-up. The median time to progression was 4.8 years. The overall risk of progression was 10% per year for the first 5 years, 3% per year for the next 5 years, and only 1% per year beyond 10 years of follow-up. Because the serum M-protein concentration and the proportion of BMPCs emerged as the most important independent risk-factors for progression, a risk-stratification model of three groups based on these two parameters was built (group I, 106 patients with serum M-protein $\geq$ 3 g/dL and $\geq$ 10% BMPC; group II, 142 patients with a serum M-protein < 3 g/dL and $\geq$ 10% BMPC; and group III, 37 patients with a serum M-protein $\geq$ 3 g/dL and < 10% BMPC). The median TTP for groups I, II, and III was 2, 8, and 19 years, respectively (Fig 1).¹² The critical factor for progression is the plasma cell number in that the extent of BMPC involvement is even more critical than the M-protein size.¹²

Fig 1. Probability of progression to active myeloma or primary amyloidosis in patients with smoldering multiple myeloma among three risk groups: group 1 (bone marrow plasma cells $\geq$ 10%, M-protein level $\geq$ 3 g/dL), group 2 (plasma cells $\geq$ 10%, M-protein level < 3 g/dL), and group 3 (plasma cells < 10%, M-protein level $\geq$ 3 g/dL). With permission of the *New England Journal of Medicine*, Kyle et al.¹²

Fig 2. Risk stratification based on bone marrow plasmacytosis, serum M protein, and serum immunoglobulin free-light chain (FLC) ratio. Patients are assigned 1 point for meeting each of the following criteria: bone marrow clonal plasma cells $\geq 10\%$; serum M protein ≥ 3 g/dL; and serum immunoglobulin FLC ratio either less than 0.125 or > 8 . The median times to progression for 1, 2, or 3 risk factors are 10, 5.1, and 1.9 years, respectively. This research was originally published in *Blood*. Dispenzieri A, Kyle RA, Katzman JA, et al: Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood* 111:785-789, 2008. © American Society of Hematology.¹³

Abnormal free light chain ratio. Considering that the free light chain (FLC) ratio is an independent predictor for progression in MGUS,²³ Dispenzieri et al¹³ investigated the potential predictive value of FLC ratio in order to try to further refine the prognosis in the Mayo Clinic series of SMM.¹² The incorporation of the FLC ratio at break-points lower than 0.126 or higher than 8 resulted in an improved prognostic classification with an even more balanced distribution of patients (Fig 2).¹³ Why an excess of clonotypic FLC is predictive for a poorer outcome in SMM is unclear, but in any event, it has become a useful and simple predictor of outcome in asymptomatic monoclonal gammopathies.^{13,23}

Immunophenotyping and immunoparesis. Pérez-Persona et al¹⁴ have shown that the presence of an aberrant phenotype of the BMPC ($\geq 95\%$ phenotypically abnormal plasma cells by multiparameter flow cytometry, defined as overexpression of CD56 and CD19 and CD45 negative and/or decreased reactivity for CD38) was the most important predictor for early progression from SMM to active MM. The cumulative progression rate at 5 years was 64% versus 8% for the patients with $\geq 95\%$ abnormal phenotype or less, respectively.¹⁴ In this study, the existence of immunoparesis (ie, decrease in one or two of the uninvolved immunoglobulins), also emerged as a significant prognostic parameter with multivariate analysis. Based on these two parameters (percent of aberrant BMPC and immunoparesis), a scoring system for patients with SMM was proposed resulting in a prognostic stratification of SMM in three groups with a cumulative probability of progression at 5 years of 4%, 46%, and 72% when none, one, or two factors, respectively, were present.

Pattern of evolution. Rosiñol et al⁹ have recognized two types of SMM according to the evolution pattern: the so-called evolving and the nonevolving. Patients with the evolving type had a progressive increase in the serum M-protein value (increase in the M-protein level in each of the first two follow-up consecutive visits) until symptomatic myeloma developed, whereas patients with the nonevolving type had a

Fig 3. Evolution of the serum M-protein levels in patients with (A) evolving smoldering myeloma and (B) nonevolving myeloma. With permission of the *British Journal of Hematology*, Rosiñol et al. © Blackwell Publishing Ltd.⁹

stable serum M-protein value until the development of symptomatic myeloma (Fig 3). Patients with evolving SMM have a shorter time to progression to symptomatic MM than patients with the nonevolving type (median, 1.3 v 3.9 years).⁹ Of interest, almost 60% of patients with evolving SMM had a previously recognized long-lasting MGUS that also had an evolving pattern,²⁴ whereas a previous MGUS was uncommon in patients with nonevolving SMM.⁹ It was also found that this different natural history correlated with a different pattern of cytogenetic abnormalities detected by comparative genomic hybridization (CGH).²⁵ Thus, the CGH pattern in evolving SMM is similar to the CGH pattern observed in patients with symptomatic de novo MM with a high frequency of chromosomal losses and 1q gains,²⁶ whereas chromosomal losses were uncommon in the nonevolving group and none of the patients in this group showed 1q gains.²⁵ It seems that a second hit is necessary for progression in the nonevolving SMM.

The most relevant current predictors of progression in SMM are summarized in Table 4.

PATTERN OF PROGRESSION TO SYMPTOMATIC MYELOMA AND INDICATIONS TO START TREATMENT

Smoldering myeloma resembles MGUS in that it is an asymptomatic monoclonal gammopathy but SMM has a significantly higher probability of progression to active MM or AL (actuarial probability at 20

Table 4. New Predictors of Progression in Smoldering Multiple Myeloma

Plasma cell mass ¹²
M-protein concentration
Proportion of BMPC
Free light chain immunoglobulin ratio ¹³
Aberrant immunophenotype and immunoparesis ¹⁴
≥ 95% BMPC with abnormal phenotype
Decrease of one or two of the uninvolved immunoglobulins
Evolution pattern: evolving versus nonevolving ⁹
Abbreviation: BMPC, bone marrow plasma cells.

years of follow-up of 78% v 21% for SMM and MGUS, respectively; Fig 4).^{12,15} It is of interest that in the Mayo Clinic study on SMM the dynamics of tumor progression during the first 1 to 2 years of follow-up constituted a key factor for progression.¹² This is in contrast with the MGUS series from the same institution in which the risk of transformation remained constant over time.¹⁵

Most patients with SMM progress with increasing anemia and/or skeletal involvement consisting of bone lytic lesions and/or diffuse osteoporosis.^{3,5-7,9} In the experience of the authors, progressive disease with impairment of renal function, extensive bone involvement, hypercalcemia, and/or extramedullary plasmacytomas is unusual.⁹ The absence of extensive skeletal involvement, hypercalcemia, or extramedullary disease is consistent with a lower proliferative activity in SMM, even at the time of disease progression.⁹ These observations support the safety of a watch and wait approach in the management of patients with SMM.^{1,2,9,19,27}

Patients who develop bone pain due to skeletal involvement, anemia, or any other end-organ damage should be treated. Concerning anemia, it is defined by the IMWG as either a Hb level lower than 2 g/dL below the normal limit or lower than 10 g/dL. However, the authors of this review have seen patients with SMM with a Hb level between 9 and 10 g/dL with no need for cytotoxic therapy for several years. It must be considered that in patients with a high serum M-protein there is also a component of hemodilution, and so the severity of anemia may be overestimated. In patients with stable level of

Hb between 9 and 10 g/dL, a watch and see approach can be considered while a continued decrease in the Hb level will be a clear indication for initiation of cytotoxic therapy. The use of erythropoietin to correct a low or decreasing Hb should be used with caution and include careful observation since this could otherwise mask disease progression, although such a treatment approach may be warranted, especially in patients with comorbidities, such as cardiopulmonary disease.

POSSIBLE TREATMENT STRATEGIES TO DELAY PROGRESSION

Alkylating Agents and Corticosteroids

There are three small studies comparing immediate therapy with melphalan and prednisone (MP) versus observation in patients with SMM.²⁸⁻³⁰ Hjorth et al²⁸ performed a randomized trial comparing immediate therapy with MP versus observation until progression in a series of 50 patients with SMM: 25 were allocated to MP and 25 to observation. In the observation arm the median time to progression was 12 months; the reason for treatment was increase in M-protein size in eight patients, development of symptomatic bone disease (bone pain, osteolytic lesions and/or hypercalcemia) in nine patients, and decrease of the Hb level to lower than 10 g/dL in the remaining five patients. In seven of 14 patients who developed progressive bone disease or anemia, the M-protein did not increase at the time of progression.²⁸ The response rate to therapy in patients treated at diagnosis was similar to that of those who received deferred therapy at the time of progression (52% v 55%). There were no significant differences in duration of response and in overall survival between the two groups. In the study by Grignani et al,²⁹ which included 44 patients with SMM, the survival of patients allocated to MP versus that of those in the observation group was similar (median, 54 v 58 months). Riccardi et al³⁰ reported 145 cases of stage I multiple myeloma who were randomly assigned to melphalan and prednisone or no treatment. There was no difference in survival (median, 64 v 71 months).

Thalidomide

Thalidomide is an antiangiogenic agent effective in the treatment of MM.³¹⁻³⁴ The action of thalidomide in MM appears to be dependent on the homing of myeloma cells in the bone marrow and on its interactions with the bone marrow microenvironment. This is supported by the lack of response of soft-tissue plasmacytomas to thalidomide.³⁵ With this background, a disease such as SMM in which the malignant plasma cells are confined to the bone marrow with no extramedullary spread could be a model highly sensitive to thalidomide.³⁴ In fact, two phase II trials, one from the Mayo Clinic,³⁶ including 29 patients, and other from the M.D. Anderson Cancer Center,³⁷ including 28 patients, showed a partial response (PR) rate of 34% and 36%, respectively. In both trials the toxicity associated with thalidomide consisted of peripheral neuropathy, somnolence, fatigue and constipation. More recently, Barlogie et al³⁸ reported the results of other phase II trial in 76 patients with SMM treated with thalidomide at an initial dose of 200 mg/d. At four years from enrollment the ≥ PR rate was 42% (PR, 25%; near complete response [CR], 12%; CR, 5%) with median times to response of 1 to 2 years. The median time to progression was 7 years. The development of peripheral neuropathy was a major problem in long-term thalidomide therapy, with dose reduction in 86% and drug discontinuation in 50%. The authors of

Fig 4. Probability of progression to active myeloma or primary amyloidosis in patients with smoldering multiple myeloma or monoclonal gammopathy of undetermined significance (MGUS). With permission of the *New England Journal of Medicine*, Kyle et al.¹²

the three studies³⁶⁻³⁸ emphasized that although thalidomide could prolong the TTP, this drug cannot be recommended for the treatment of SMM until a benefit is shown in prospective randomized trials.

Bisphosphonates

Treatment with bisphosphonates reduces skeletal-related complications in patients with MM.³⁹ It has been shown that bisphosphonates can have an antitumor effect through different mechanisms: induction of apoptosis; modulation of adhesion molecules; and expansion of cytotoxic gamma/delta T cells.⁴⁰ In addition, three patients with SMM in whom the serum M-protein was significantly reduced with the use of pamidronate alone have been published.^{41,42} However, a small trial from Spain including 12 patients with SMM, showed that pamidronate induced bone formation, but without any antitumor effect.⁴³ In the same context, a large randomized Italian study showed that pamidronate therapy significantly reduced the number of skeletal events but no significantly prolongation of TTP or overall survival in patients with early-stage myeloma was seen, although the follow-up was relatively short.⁴⁴ The same Italian group has since reported that in patients with SMM, treatment with zoledronic acid in a large, randomized trial also significantly reduced the number of skeletal events by the time of progression, but had no apparent effect on overall survival.⁴⁵ While the potential toxicities of bisphosphonates, such as renal injury and osteonecrosis of the jaw, should be taken into account, these data suggest potential benefit for patients with early bone disease, such as MM-related osteopenia.

Serum levels of interleukin 1 beta (IL1- β) constitute a marker of progression in asymptomatic monoclonal gammopathies.⁴⁶ With this background, a trial using the antagonist of the receptor of IL1- β was activated in 47 patients with SMM.⁴⁶ The median PFS for patients with or without decrease in C-reactive protein serum levels was more than 3 years versus 6 months, respectively ($P = .002$). These results indicate that the antagonist of IL1- β receptor may prolong the TTP in SMM through the inhibition of IL-6 production, and suggest that further trials of this approach are warranted.

Ongoing Clinical Trials

Several clinical trials are ongoing to determine if progression of SMM can be delayed or halted. A randomized trial is ongoing at the Mayo Clinic comparing thalidomide plus zoledronic acid versus zoledronic acid alone. No results are yet available. Randomized trials comparing lenalidomide versus observation are being planned by the Eastern Cooperative Oncology Group and the Southwest Oncology Group. A Spanish Programa de Estudio y Tratamiento de las Hemopatías Malignas trial is comparing lenalidomide plus low-dose dexamethasone versus observation in patients with high-risk SMM (ie, serum M protein ≥ 3 g/dL and $\geq 10\%$ BMPC or one of the above plus $\geq 95\%$ plasma cells with aberrant immunophenotype and immunoparesis). Another multicenter study is investigating the biologic activity and clinical efficacy of the cyclo-oxygenase 2 inhibitor, celecoxib. Until the results of additional randomized trials are available, observation remains the standard of care in SMM.

RESPONSE TO THERAPY AND OUTCOME AFTER PROGRESSION

In patients with SMM who then evolve into symptomatic MM the response rate to chemotherapy has ranged from 52% to 64%.^{3,5,7,28}

However, no data on the degree of response was given in the above series. In the series by Rosiñol et al,⁹ the overall response rate was 63%. However, only 43% achieved PR, whereas 57% of the patients showed minimal or no response to their initial chemotherapy. Patients with evolving SMM had a trend toward a higher PR rate than those with the nonevolving type (53% v 21%; $P = .08$).⁹ It is of note, that in the group of deferred therapy until progression in the series by Hjorth et al²⁸ a significantly higher response rate was observed among patients in whom the M-protein size increased by at least 25% as compared to those who had clinical progression while maintaining a stable M-protein (81% v 27%; $P < .01$). It could be speculated that patients showing an increase in the M-protein size at the time of progression correspond to the evolving type in the Rosiñol et al⁹ series. In aggregate, it seems that the response to therapy after progression in the nonevolving SMM is characterized by a relatively modest tumor reduction or no significant change. However, despite this modest effect from therapy the median survival after progression remains about 3.5 years in both subsets of SMM, which is comparable to that reported in the general myeloma population. Of interest, patients who had a previously recognized MGUS or SMM and who were included in a tandem transplant program (total therapy II) at the University of Arkansas, had a significantly lower CR rate compared with patients with the novo MM.⁴⁷ In this trial, however, the lower CR rate did not adversely affect survival. Finally, in another study by the same group, a gene-expression signature of monoclonal gammopathy of undetermined significance appeared to be linked to good prognosis.⁴⁸ All the above data support the notion that the more indolent nature of SMM may persist even after progression, and so confer a more favorable outcome.

FOLLOW-UP RECOMMENDATIONS

There are no formal guidelines concerning evaluation and follow-up for patients with SMM. A recommended work-up at baseline in patients with suspected SMM is summarized in Table 5. Although data are lacking to effectively guide the frequency of follow-up and the specific testing warranted, a reasonable approach for a patient in whom SMM is suspected is a repeat clinical examination in 3 months

Table 5. Recommended Work Up at Baseline in Patients With Suspected Smoldering Multiple Myeloma

Medical history and physical examination
CBC
Serum calcium and creatinine
Protein studies
Total serum protein and serum electrophoresis (serum M-protein quantitation)
24-h urine protein electrophoresis (urine M-protein quantitation)
Serum and urine immunofixation
Serum free light chain measurement (FLC ratio)
$\beta 2$ -microglobulin
Bone marrow aspirate
Skeletal survey
MRI of thoracic-lumbar spine and pelvis

Abbreviations: FLC, free light chain; MRI, magnetic resonance imaging.

with CBCs and biochemical survey including serum creatinine, calcium, and albumin plus the Hb level and serum and urine M-protein levels. If the results show that the disease is stable, the diagnosis of SMM is confirmed and the subsequent follow-up should be planned at 3-month intervals for the first year in order to establish the pattern of evolution (evolving v nonevolving). As the current definition SMM is heterogeneous, thus resulting in a variable prognosis, particular attention must be paid to those patients with higher risk of early progression (ie, high plasma cell mass M-protein ≥ 3 g/dL and $\geq 10\%$ BMPC, $\geq 95\%$ phenotypically abnormal BMPC, immunoparesis, or evolving type). In contrast, for patients at a lower risk of progression (ie, those with only the M-protein or the percentage of BMPC criteria but not both—risk groups II and III in the Kyle study, group I according to the Salamanca criteria— $< 95\%$ phenotypically aberrant plasma cells with no immunoparesis, the nonevolving type as well as those beyond 5 years from diagnosis) a less frequent follow-up could be enough.

Patients should be informed that currently there is no indication for immediate treatment but that they will likely require therapy in the future. Pneumococcal vaccination may be helpful, particularly in patients with high IgG levels and decrease of IgA and/or IgM.⁴⁹ Only when there is a reasonable suspicion of progression a full evaluation, including bone marrow aspirate and skeletal survey, should be done. Patients should not be treated until progressive disease with end-organ damage is evident. This is particularly important in patients with the nonevolving type who have a median time to progression of 4 years. It is less important in the evolving variant with median TTP of about 1.5 years. A progressive decrease in the Hb level is the most frequent and reliable indicator of progression. Other indicators of progression that mandate treatment are the development of soft-tissue plasmacytomas or significant skeletal involvement as well as increased serum calcium or a rise in the serum creatinine level.^{11,50} While the characterization of SMM by molecular genetic studies will

likely result in a more accurate risk stratification, the recently recognized predictors of outcome will be helpful for better monitoring and for the investigation of treatment approaches with new noncytotoxic drugs aimed at delaying progression. In this regard, the end points by a consensus panel for clinical trials in different settings of myeloma have been reported.⁵⁰ The panel recommended improvement in OS as one of the most clinically meaningful and important is SMM, and emphasized the importance of minimizing toxicity in this population as well as exploring strategies to improve quality of life.

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