

What is new in MGUS and smoldering multiple myeloma

M. Vercruyssen¹, L. Vrancken², J. Caers²

SUMMARY

Multiple Myeloma (MM) and other plasma cell malignancies initially present as an asymptomatic precursor state, known as monoclonal gammopathy of undetermined significance (MGUS). When confronted to a monoclonal protein in blood or urine tests, physicians should first exclude the presence of a treatment-requiring MM. They should be aware that there are two benign precursor states, that do not require anti-myeloma treatment. Both MGUS and Smoldering Multiple Myeloma (SMM) need an initial visit by a haematologist, with further follow-up tailored to the individual patient and disease characteristics. In the current article we describe both entities, discuss their monitoring and resume the latest publications in their field.

INTRODUCTION

In 2014, the International Myeloma Working Group (IMWG) updated the diagnostic criteria for Monoclonal Gammopathy of Undetermined Significance (MGUS), Smoldering Multiple Myeloma (SMM) and multiple myeloma (MM).¹ The distinction between the different disease stages is based on biological parameters and the presence of clinical symptoms or early signs of emerging myeloma disease (*Table 1*). MGUS is defined by a serum M-protein level of <3 g/dL, a bone marrow plasma cell (BMPC) infiltration of $<10\%$, and the absence of clinical complications. SMM is defined by serum M-protein (IgG or IgA) levels of ≥ 3 g/dL and/or clonal BMPCs of 10%-60% in the absence of a myeloma defining event (MDE) or amyloidosis.² The updated IMWG diagnostic criteria for MM include the presence of M-protein in blood or urine, a BMPC infiltration of $>10\%$, or biopsy-proven bony or extramedullary plasmacytoma as well as a MDE. A MDE is defined by CRAB criteria (hypercalcemia, radiological bone lesions, anaemia, and renal failure) or one or more of the following biomarkers of malignancy: a clonal BMPC percentage of $>60\%$, involved/uninvolved serum free light chain (sFLC) ratio of >100 or >1 , and focal lesions (FLs) detected by magnetic resonance imaging (MRI).

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

The incidence of MGUS is estimated at 3.4% in the general population over 50 years of age. This incidence increases with age from only 1.7% in patients aged 50-59 years to 6.6% beyond 80 years.³ Several hereditary, genetic as well as environmental factors play a role in the development of MGUS, including age, race, gender, familial history and obesity. A recent French study demonstrated that the M-protein isolated from MGUS and MM patients, reacted in 57 (23.4%) of 244 patients studied with lysates or proteins from infectious pathogens. Of these, EBV nuclear antigen-1 (EBNA-1) was the most frequent target.⁴ These results indicate that antigen-driven stimulation of plasma cells could be an early pathogenic mechanism that initiates monoclonal gammopathies.

RISK OF PROGRESSION OF MGUS

The average risk of evolution from MGUS to MM, amyloidosis or other lymphoproliferative disease is 1% per year, depending on the nature of the protein implicated (IgG or non-IgG), the monoclonal protein level (> 15 g/l) and the FLC ratio (abnormal or not).^{5,6} Using these three items, the Mayo Clinic developed a simple score that allows to stratify patients

¹Service d'Hématologie, Institut Jules Bordet; ²Service d'hématologie, CHU de Liège.

Please send all correspondence to: Dr. Jo Caers, MD, PhD; Department of Clinical Hematology, Centre Hospitalier Universitaire de Liège, Dom Univ Sart Tilman - B 35, B-4000 Liège, Tel: +32 (0)4 3667704, Secr: +32 (0)4 3667201, Email: jo.caers@chu.ulg.ac.be

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TABLE 1. The differential diagnosis between MGUS, Smoldering Myeloma and Multiple myeloma. The discrimination between these monoclonal gammopathies is based on (1) the plasma cell infiltration in the bone marrow, (2) the presence of clinical symptoms related to myeloma disease and (3) existence of biomarkers of disease that allow initiation of treatment.

	MGUS	SMM	MM	
			Biomarker	CRAB
M-protein < 30 g/l	} →			
BM PC < 10%				
M-protein > 30 g/l	→			
BM PC > 10%	→			
BM PC > 60%	- - - - -		→	
FLC ratio > 100	- - - - -		→	
MRI ≥ 2 focal lesions	- - - - -		→	
Hypercalcaemia	→			→
Renal failure	→			→
Anaemia	→			→
Bone disease	→			→

Abbreviations. MGUS: monoclonal gammopathy of undetermined significance, SMM: smoldering multiple myeloma, MM: multiple myeloma BM: bone marrow, PC: plasma cells, FLC: free light chain, MRI: magnetic resonance imaging (adapted from ²⁰)

according to their risk status: eg 5% of the patients that do not show any risk factors progress at 20 years. This percentage increases to 58% if three factors are present.⁶ Of note, if the FLC ratio is very abnormal (< 0.125 or > 8), the risk of progression is even higher, reaching 60.5% at 20 years.⁶ Another significant risk factor of progression is a decreased serum level of both uninvolved immunoglobulins (Hazard Ratio of 2) while a decrease in just one of them does not impact this risk.⁷ Recently, two different teams showed that also the presence of translocation (4;14) and deletion 17p in the bone marrow clonal plasma cells is associated with a higher risk of progression.^{8,9} As such, when feasible, cytogenetics may allow the identification of a high-risk patient group for whom a closer follow up might be beneficial.

MONITORING OF MGUS PATIENTS

While MGUS is relatively frequent, in the absence of symptoms the work-up rarely leads to the diagnosis of an overt disease. Moreover, it is not certain that close follow-up, and an early diagnosis of MM, leads to a better prognosis, since

more than one third of the MGUS cases evolve to SMM and do not require any treatment.¹⁰ Furthermore, the vast majority of the MGUS patients will die from other diseases. As such, after the identification of the risk group and exclusion of any evolution after three months, one could refer the patient to his general practitioner for a follow-up every 2 or 3 years or annually in case of one or more risk factors. Moreover, if life expectancy is less than 5 years and/or the patient is older than 85 years, the follow-up can be omitted.¹¹ If a progression is suspected, of course, the patient should be referred to the haematologist for further investigations. To identify progression to myeloma or lymphoma, biological and radiological tests are generally required to identify a disease progression. However a careful clinical examination is needed to exclude complication of the monoclonal protein itself. Once the work-up has established the absence of these pathologies and the early follow-up did not show a rapid evolution of the paraprotein, the patient can be referred to his general practitioner to assure the right follow-up (Figure 1).

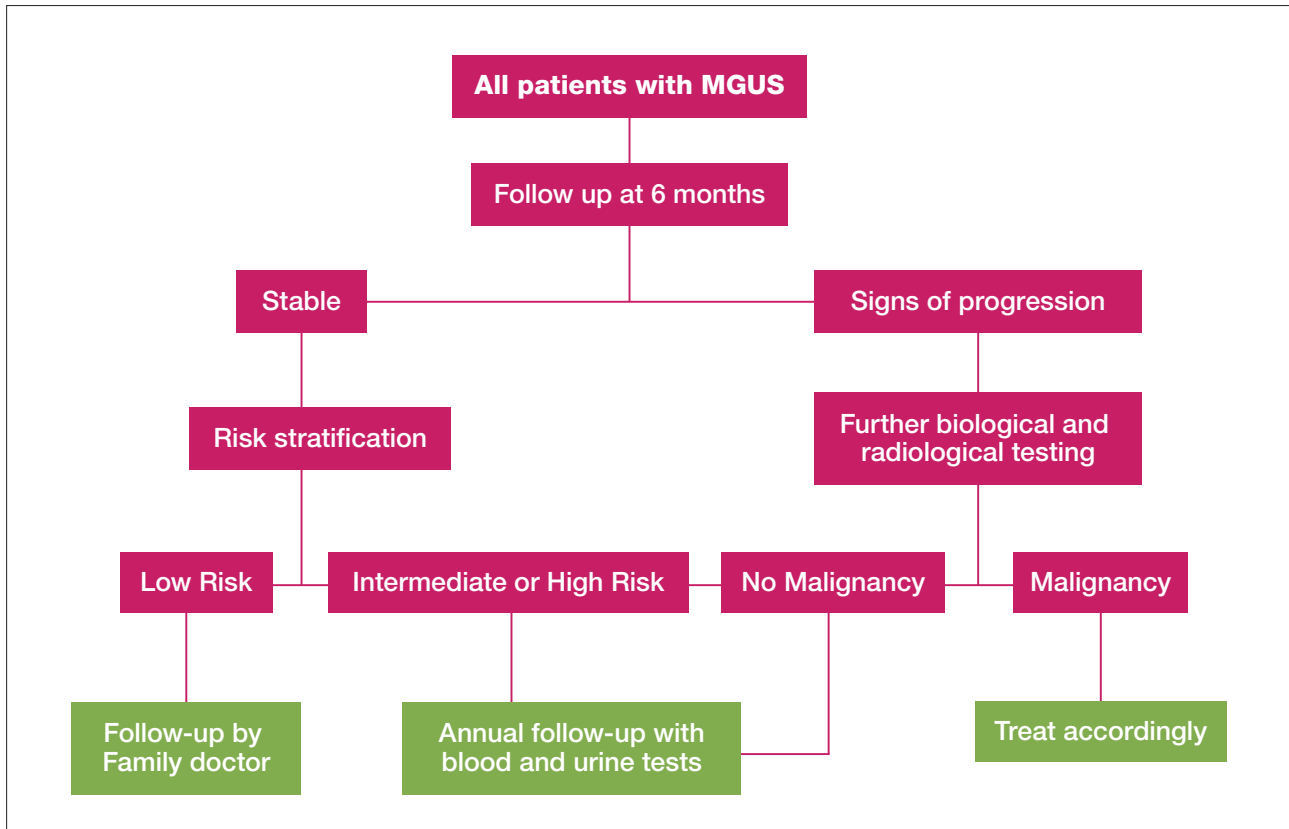


FIGURE 1. Algorithm for follow-up of patients with monoclonal gammopathy of undetermined significance (MGUS).

MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE: A NOVEL CONCEPT

Signs or symptoms of a peripheral neuropathy must be investigated to exclude paraneoplastic syndrome, in particular if IgM is the paraprotein implicated since the prevalence of symptoms can reach 31% versus only 6% in case of IgG subtype.¹² Fifty percent of them are due to anti-MAG (myelin-associated glycoprotein) activity of the M component and another 35% is related to anti-ganglioside activity. Amyloidosis or POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein and Skin change) must also be evoked, especially in case of lambda secretion.¹² In case of a creatinine increase, myeloma or progression to myeloma must be excluded, but other, sometimes discrete but always severe troubles can emerge. This includes nephrotic syndrome in amyloidosis or in other light or heavy chain deposits (Randall type). Fanconi disease, caused by light chain deposits in the renal tubules, must also be recognised in case of ionic and metabolic abnormalities. Other paraneoplastic immune glomerulonephritis can also be observed. All these entities are known as MGRS (Monoclonal Gammopathy of Renal Significance) as the abnormalities can be proved to be related to the monoclonal pattern. A treatment could be envisaged. So, in front of an unexplained

renal impairment, further investigations must be performed and a kidney biopsy deserves serious discussion.¹³ Some dermatologic entities are also described. The Schnitzler syndrome which manifests with fever, urticarial rash and arthropathy (sometimes with organomegaly) is caused by a monoclonal IgM paraprotein, especially kappa. Other skin diseases can be encountered, such as necrobiotic xanthogranuloma or other skin changes, in particular in the POEMS syndrome. Finally, some haemorrhagic status can be observed in case of paraneoplastic deficiency of von Willebrand factor or factor X in amyloidosis.

SMOLDERING MULTIPLE MYELOMA

In contrast to MGUS, SMM has a higher risk of progression to symptomatic MM. However, both diseases are considered as precursor disease stages and, by definition, both disorders are asymptomatic. The 2014 IMWG criteria, changed the group of ultra-high risk SMM (which was associated with an 80% risk of progression to MM) into the group treatment-requiring MM.¹ This change allows physicians to initiate an early therapeutic strategy, that could avoid serious complications and where the potential benefit justifies the risks of toxicity.

TABLE 2. Prognostic factors of high-risk SMM (partial list).

Serum M-protein ≥ 30 g/L
IgA SMM
- Progressive increase in M-protein level (evolving type of SMM; increase in serum M-protein by $\geq 25\%$ on 2 successive evaluations within a 6-month period) - Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes
Abnormal PC immunophenotype ($\geq 95\%$ of BMPCs are clonal)
t(4;14) or del(17p) or 1q gain
Increased circulating PCs
MRI with diffuse abnormalities or 1 focal lesion
PET with hypermetabolic focal lesions, but without underlying bone lytic lesions

RISK OF PROGRESSION OF SMM

The risk of progression of SMM was originally established by Kyle *et al.* based on a cohort of 236 patients with smoldering myeloma disease, defined by the old IMWG criteria.¹⁴ The estimated risk of progression to MM or amyloidosis was 10% per year for the first 5 years, then the progression rates decreased progressively, but after 20 years 72% of the patients progressed. The recent IMWG criteria consider ultra-high risk SMM as treatment-requiring MM. As such, this group of patients is no longer considered as SMM patients, which probably affects the initial progression risks that were described by Kyle *et al.* Prospective studies are needed to reassess this risk when the 2014 IMWG criteria are applied.

In the past decades, other prognostic factors that identified patients with a high risk of progression have been described. These risk factors are summarized in Table 2. Patients that do not present any of these risk factors can be considered as low-risk patients, with an estimated risk of progression of 5 to 10% per year. Some of these factors are based on routine tests, while others require complementary examinations. Routinely performed radiological and laboratory tests (immunoglobulin isotype, serum M-protein levels, sFLC levels, immunoglobulin quantification) can help to estimate this progression risk in daily practice. The use of cytogenetic evaluation is justified for young patients, but there is insufficient data to justify the systematic realization of a PET-CT for every patient with SMM.

Researchers at the Mayo Clinic re-examined their cohort of patients with SMM who met the 2014 IMWG criteria to define their natural history and identified several risk factors for progression.¹⁵ They finally proposed a simple scoring system, that can be retained as the “3 X 20” score. A bone marrow plasmacytosis superior to **20%**, M-protein levels above **20 g/L**, and a sFLC ratio above **20** at diagnosis can be used to risk stratify patients with SMM using the current IMWG criteria. The estimated median time to progression in the low-risk, intermediate-risk, and high-risk groups were 109.8 months, 67.8 months and 29.2 months, respectively.

MONITORING OF SMM PATIENTS

Similar to MGUS patients, the monitoring of SMM is based on clinical (paying attention to signs of a possible MM) and biological (blood counts, calcemia, serum creatinine, protein electrophoresis, proteinuria) follow-up (Figure 2).¹⁶ High-risk patients need to be followed-up closely (every 3 months) to allow the early detection of an evolution towards symptomatic MM and to avoid devastating complications such as acute renal failure, vertebral fractures, spinal cord compression, etc. For these patients, sFLC assays and MRIs can be repeated during the follow-up, although there is no standardised recommendation on the frequency and intervals of these tests. For low-risk SMM patients, the monitoring can be delayed (every 6 months) and complementary studies such as sFLC and MRI should be repeated in case of signs of progression. We believe that prospective studies are needed to define the best monitoring strategies for both SMM patient groups.

EARLY TREATMENT OF HIGH-RISK SMM?

After the landmark publication of Mateos *et al.*, other clinical trials evaluating early treatment strategies for high-risk SMM have been presented.¹⁷ These trials either aim at curing patients with aggressive treatments or to control and delay progression with a prolonged treatment. Preliminary results from 2 studies were presented at ASH 2017. Mateos *et al.* presented the preliminary results of the GEM-CESAR study, a phase II single-arm trial including 90 patients with a high-risk SMM (defined according to the prognostic scores of the Mayo Clinic and/or of the Spanish Myeloma Group).¹⁸ The treatment in this trial consisted of carfilzomib, lenalidomide and dexamethasone (KRd) as induction, followed by HDT-ASCT and consolidation with Krd and Rd maintenance. It has to be acknowledged that 30 patients (33%) presented at least one of the new MM diagnostic criteria of 2014. The primary endpoint was the achievement of minimal residual disease (MRD) negativity (evaluated by flow cytometry). At the time of the analysis, most patients (N=71) completed the 6 induction cycles, 42 had received intensification, 35 had

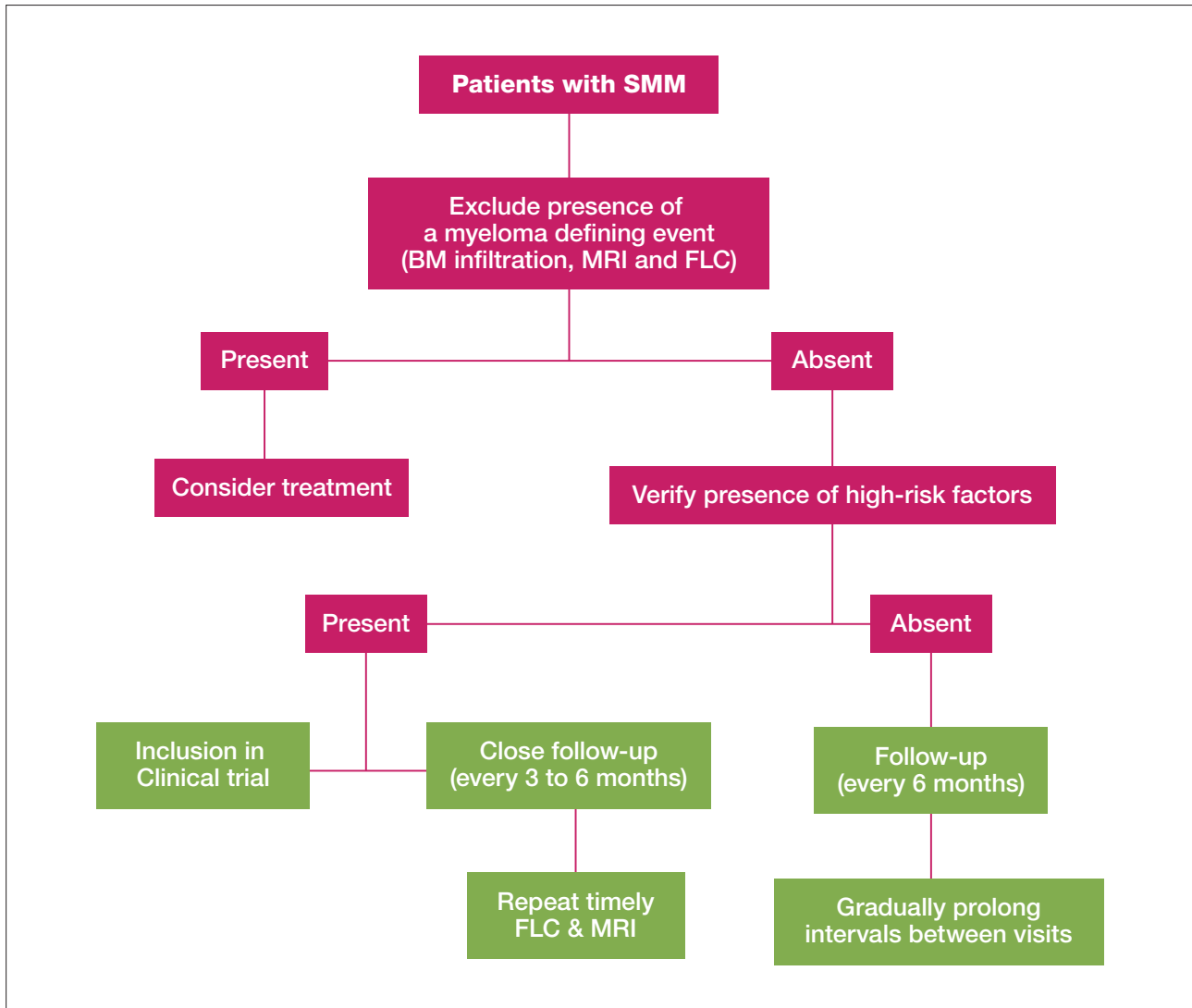


FIGURE 2. Algorithms for patients with smoldering multiple myeloma (SMM).

received consolidation, and 29 were in the maintenance phase. After a median follow-up of 10 month, 69 patients (98%) responded to treatment after the completion of induction therapy, about half of whom had a complete response (CR) or stringent CR (sCR). Two patients obtained a CR but relapsed before the end of induction. MRD negativity and depth of response to treatment increased as patients progressed through therapy. After the consolidation phase, 60% of the patients achieved MRD negativity, indicating that deep responses can be obtained with an intensive treatment of SMM.¹⁸ Of course, longer follow-up data are needed to assess if this strategy will ultimately cure patients.

Hofmeister *et al.* presented the preliminary results of the CENTAURUS trial, a randomized phase II study evaluating 3 daratumumab dose schedules in 123 SMM patients.¹⁹ There were 3 treatment strategies, all including cycles of 8 weeks of treatment: (1) a short regimen consisting of 1 cycle of

daratumumab weekly; (2) an intermediate schedule starting with weekly daratumumab in cycle 1 and every 8 weeks up to cycle 20 and (3) a long regimen (weekly daratumumab in cycle 1, every other week in cycles 2 and 3, every 4 weeks in cycles 4 through 7, and every 8 weeks up to cycle 20). The two main endpoints were CR rate and progression-free survival (PFS). The 12-month PFS rates were 95% with the long schedule, 88% with the intermediate dosing schedule, and 81% with the short, intense schedule. More than half (54%) of the patients in the long arm and 49% in the intermediate arm had a partial response (PR) or better. In the short arm, 38% of patients achieved a PR or better. The CR rate was less than 15% in each arm. These results show that daratumumab in monotherapy may induce a haematological response and delays the progression of high-risk SMM. However, it also suggests that the treatment should be extended as shown by the poor results in the short arm. It is unlikely that dara-

tumumab single-agent will cure high-risk SMM, but it may delay the progression of the disease. The long dosing schedule is currently under investigation in the ongoing phase III AQUILA study.

Both these approaches (intensive vs. extended treatment) are interesting, but they also have their limitations. Additionally, some questions remain unanswered: what will be the relapse rate after the intensive treatment?; How will relapsing patients respond to their subsequent treatment? Similar questions can be proposed regarding the daratumumab-treated patients. Taking into account these question, it is important to restrain these approaches to patients with a high-risk of progression that justifies a therapeutic intervention.

CONCLUSIONS

MGUS is a frequent abnormality especially in the older population. In most cases, its diagnosis is accidental and the work-up will rarely lead to the diagnosis of an overt malignancy. The general risk of progression is 1% per year, but should be adapted to every individual situation, depending on the different known factors but also with the help of the cytogenetic tools if possible. More caution is needed in the follow-up of SMM patients who have a higher risk of progression to MM. The recent IMWG criteria redirected ultra-high risk SMM patients to treatment-requiring MM patients.

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