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BSH GOOD PRACTICE PAPER

Diagnosis and management of smouldering myeloma: A British Society for Haematology Good Practice Paper

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METHODOLOGY

This good practice paper was compiled according to the British Society for Haematology (BSH) process at (https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate the levels of evidence and to assess the strength of recommendations. The BSH produces good practice papers to recommend good practice in areas where there is a limited evidence base, but for which a degree of consensus or uniformity is likely to be beneficial to patient care.

Literature review details

A literature search was performed using the EMBASE and MEDLINE databases using the following search terms: monoclonal gammopathy of undetermined significance, multiple myeloma, smouldering (smoldering) multiple myeloma; monoclonal gammopathy, MGUS.

Review of the manuscript

Review of the manuscript was performed by the BSH Haemato-Oncology Task Force, the BSH Guidelines Committee and the Haemato-Oncology sounding board of BSH. It has also been reviewed by the UK Myeloma Society and Myeloma UK.

INTRODUCTION

Multiple myeloma (MM) is a clonal bone marrow disorder of plasma cells. MM is preceded by the precursor conditions monoclonal gammopathy of undetermined significance (MGUS) and smouldering myeloma (SMM). SMM sits between MGUS and MM, representing a plasma

cell clone (10%–59%) without organ or tissue impairment. In retrospective data, prior to the updated IMWG criteria, the risk of SMM progressing to MM or a related disorder is 10% per year for the first 5 years after diagnosis, 3% per year for the next 5 years and 1% per year for the next 10 years[1] with biological behaviour ranging from MGUS to high-risk MM.[2] The time of diagnosis is, however, random given that it is an asymptomatic condition, and therefore, most patients will have had SMM for some unknown time before diagnosis. Similar genetic changes are detected in MGUS, SMM and MM and include hyperdiploidy (typically trisomies of odd chromosomes 3, 5, 7, 9, 11, 15, 19, 21) or translocations involving the immunoglobulin loci (common translocation partners: *MMSET/FGFR3, CCND1, CCND3, MAF, MAFB1*).[3–6] Copy number alterations (commonly del(13q), gain(1q), del(14q), del(1p), del(17p))[6] and single nucleotide variants (SNVs) generally increase with progression to MM but the genomic makeup of the myeloma clone is nearly fully acquired by the time of SMM diagnosis in the majority of cases.[5,7] In keeping with the random timepoint of SMM diagnosis, using mutational signatures to reconstruct chronological development of these genetic abnormalities, some initiating translocations leading to transformation of post-germinal centre B cells may occur in the second or third decade of life.[8]

In 2014, the diagnostic criteria for MM were updated by the International Myeloma Working Group (IMWG) to include the biomarkers ≥60% clonal bone marrow plasma cells, ratio of involved to uninvolved light chains ≥100 with involved FLC >100 mg/L (using FREELITE assay), or >1 focal lesion on MRI.[9] This update was prompted by the evidence that some asymptomatic patients derived an overall survival benefit from therapy[10] and demonstration in multiple cohorts that these biomarkers were associated with an ultra-high risk of progression (>80% at 2 years).[1,9,11–18] A meta-analysis, however, has shown a significantly lower risk of progression in more recent studies of untreated patients who met the updated IMWG criteria for MM based on BMPC and SFLC.[19] The IMWG criteria relate to FLC measurements using the FREELITE assay although other FLC assays are available.

The epidemiology of SMM is poorly defined with an estimated lifetime prevalence of MM of 1% in the United Kingdom.[20] Data from the Swedish Myeloma Registry demonstrate 14.4% of patients had a diagnosis of SMM with an incidence of 0.4/100,000/year.[21] The iStopMM study offered screening to all adults over 40 years old in Iceland and included 75 422 patients and identified a much higher incidence of SMM. The overall prevalence of SMM in the population was 0.53% (95% CI 0.49–0.57%) being more common in men and increasing with age with a median of 70 years. It should be noted that this represents an ethnically homogenous, almost entirely Caucasian, population.[22] The prevalence was higher in men (0.69%) than in women (0.39%) and increased with age to 1.08% in over 70s and 1.59% in those over 80 years old.[22] The greater prevalence described in the iStopMM study may relate to the nature of population-based screening which is more accurate in identifying SMM patients, particularly with low risk SMM, than previous epidemiological studies.

Definition

Diagnosis of SMM requires evidence of[9]

1. Serum monoclonal protein ≥30 g/L or urinary monoclonal protein ≥500 mg/24 h and/or 10%–59% of clonal bone marrow plasma cells and
2. Absence of myeloma-defining events as defined by the IMWG 'SLiM CRAB' criteria (Table 1)[9]

SCREENING

The role of screening for premalignant plasma cell disorders is uncertain. A prior knowledge of MGUS and SMM reduces late presentations associated with poorer outcomes.[23,24] There is, however, currently a lack of evidence to support early intervention. The iStopMM study in Iceland will provide further information regarding potential benefits of a screening approach, but its practicality and cost-effectiveness in larger and more ethnically diverse populations remains undetermined.[22] To predict the progression of developing myeloma in a high-risk population, the PROMISE study in the USA screens people of Black ethnicity or with a family history of a haematological malignancy aged 30 years or over.[25] More trials of screening and monitoring are warranted, with the use of a targeted approach for higher risk patients to improve cost-effectiveness and continual re-appraisal of the balance between risk and benefit of screening for MGUS and SMM is required as early intervention for the condition continues to evolve.

Recommendations

- Current evidence does not support screening for MGUS and SMM outside of clinical trials (1C)

TABLE 1 SLiM CRAB criteria.

S	≥60% clonal plasma cells in bone marrow
Li	Involved to uninvolved light chain ratio >100 (with involved light chain >100 mg/L)
M	More than one focal lesion on MRI >5 mm in size
C	Hypercalcaemia (>2.75 or > 0.25 mmol/L above upper limit of normal)[a]
R	Renal impairment (serum creatinine >177 μmol/L or creatinine clearance <40 mL/min)[a]
A	Anaemia (Hb <100 or ≥20 g/L below lower limit of normal)[a]
B	One or more osteolytic bone lesion on XR, CT or PET-CT (>5 mm in size)[b]

[a]With no other cause.

[b]If <10% clonal plasma cells on bone marrow, >1 bone lesion required to differentiate from solitary plasmacytoma of bone.

Investigations at diagnosis

Patients with suspected myeloma should be investigated using the tests referred to in Table 2 including a bone marrow biopsy and cross-sectional imaging.[22–25] The criteria for suspecting myeloma are not defined but include patients with any monoclonal immunoglobulin protein and potential myeloma end-organ damage. In those patients with a monoclonal immunoglobulin protein without any features suggestive of myeloma or amyloid end-organ damage (CRAB features, unexplained proteinuria, cardiomyopathy or neuropathy), consider investigating if the following levels are found—monoclonal protein levels: IgG >15 g/L, IgA >10 g/L, monoclonal FLC >500 mg/L or profound unexplained immunoparesis. Patients with a high-risk or high–intermediate-risk MGUS should also be investigated (see MGUS guidelines[26]). The iStopMM group have published a model to predict the probability of finding ≥10% plasma cells on bone marrow examination, based on routine testing during the work-up of a suspected MGUS which may help select patients for bone marrow biopsy.[27]

Testing for urinary Bence Jones protein is no longer recommended by the British Society for Haematology (BSH)[28] or by the National Institute for Health and Care Excellence (NICE)[29] for the diagnosis of myeloma. However, analysis of a series of patients with SMM with SFLC ratio ≥ 100 showed that those with low (undetectable or <200 mg/24 h) urinary monoclonal protein excretion showed significantly lower 2-year risk of progression (13.5% vs. 36.2% in those with >200 mg/24 h), noting that even those with higher Bence Jones proteinuria had low rates of progression at 2 years compared with those previously reported and far from the threshold of 80% used to justify treatment based on the SLIM criteria.[30] Spot ±24 h urine collection for monoclonal protein excretion may be considered for prognostication in select patients with high serum light chains. Urine albumin:creatinine ratio along with troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) can be a useful screening tool for detecting amyloid and it is critical to explore amyloid as a potential diagnosis during clinical history and examination. Cast nephropathy is unusual with an involved free light chain of <500 mg/L and renal biopsy should be considered in unexplained renal impairment.[31] Imaging in myeloma is discussed in detail in recent UK and international guidelines[32–35] and cross-sectional imaging is mandatory.

As per BSH guidelines,[28] bone marrow samples should include an aspirate and trephine biopsy for plasma cell quantification as well as fluorescence in situ hybridisation (FISH)[28] to look for cytogenetic abnormalities that inform risk stratification and may influence management in the future (particularly t(4;14), del(17p) and gain(1q)). In SMM, del(13)/del(13q) is reported to be prognostic for risk of progression to MM by the IMWG and is included in the cytogenetic markers within their risk score.[36] Repeat FISH should be considered at progression in line with current recommendations for newly diagnosed MM[28]; this may be at significant time interval from initial SMM diagnosis where FISH may have been limited by lower plasma cell percentage and presence of residual non-malignant plasma cells.[37]

There remains lack of consensus as to percentage cut-off values that define a positive FISH results, affected by specificity and uncertain prognostic relevance of small clones.[28] The EMN has suggested conservative cut-offs of 10% for translocations and 20% for copy number abnormalities (CNAs) to signify positive FISH results.[38] The IMWG risk score, that incorporates FISH results, performed retrospective analysis of patient records from participating sites which had various cut-offs for FISH[36] deriving prognostic significance. We have suggested a cut-off of cytogenetic abnormalities seen in >20% of cells on FISH in line with previous BSH guidelines on the diagnosis and management of newly diagnosed MM.[28] However, many CNAs are secondary events which are often subclonal yet of relevance in driving disease progression and may be missed by overly conservative thresholds for detection cut-off.[5,39] This is complicated further in SMM by the presence of residual non-malignant plasma cells remaining after CD138-selection which may lower the number of tumour cells being examined.[37] Therefore, the prognostic significance of abnormalities in <20% of cells cannot be excluded and remains poorly understood. A targeted next-generation sequencing panel has been developed for use in myeloma and validated against whole-genome and FISH[40] and has been utilised although not validated in SMM.[39] At present, it is not in routine clinical use, but there is increasing interest in molecular profiling in this setting.

TABLE 2 Initial investigations for patients with suspected and confirmed myeloma.

Screening tests	FBC Urea and creatinine Calcium Immunoglobulins and serum electrophoresis Immunofixation of serum Serum-free light chains
Tests to establish diagnosis	Bone marrow aspirate and trephine biopsy with plasma cell phenotyping Imaging—in order of preference WB-MRI (diffusion weighted), PET-CT or low-dose WB-CT (see BSH guidelines imaging in myeloma)
Tests to estimate tumour burden and prognosis	FISH Analyses for t(4;14), t(14;16), t(11;14), 17p-, 1q+, 1p- Consider testing for t(14;20), 13q- and hyperdiploidy β2 microglobulin LDH Albumin

Recommendations

- Investigations should be based on the tests listed in Table 2. (1C)
- Serum-free light chain analysis should be used to investigate monoclonal light chains rather than urinary Bence Jones protein. (1B) However, 24-hour urine for protein and Bence Jones may help assess light chain load in uncertain

cases with high monoclonal FLC, in light chain only SMM or where there is suspicion of AL amyloidosis. (2C)
- Renal biopsy should be considered if SFLC <500 mg/L and myeloma is being considered as the cause of renal impairment. (1C)
- Cross-sectional imaging, ideally functional (i.e. diffusion-weighted whole-body MRI, which has greatest sensitivity, or PET-CT), should be used. Skeletal survey should not be used to assess bone disease in myeloma. (1A)
- Urine albumin:creatinine ratio along with troponin and NT-proBNP and careful assessment for features of amyloid can be a useful screening tool for detecting amyloid. (2C)
- All cases of newly diagnosed myeloma should be discussed at an MDT meeting. (1C)
- Cytogenetic analysis using interphase FISH on CD138-selected cells should be undertaken on all patients at diagnosis. (1A)
- Samples should be probed for t(4;14)(p16;q32), t(14;16)(q32;q23), t(11;14)(q13;q32), 17p−, 1q+, −1p and testing considered for t(14;20)(q32;q11), 13q- and hyperdiploidy. (1B)
- Cytogenetic abnormalities found in >20% of cells should be considered significant. The significance of smaller clones is not clear. (2C)

PROGNOSIS/PROGNOSTIC FACTORS/ RISK STRATIFICATION

Several validated risk scores exist with a large number of prognostic biomarkers identified. The potential advantages and disadvantages are summarised in detail in a recent review by Lussier et al.[41] and in Table 3. Although models continue to evolve and are imperfect at distinguishing progressors from non-progressors within 2 years, the current iterations are useful to guide patient counselling and practical management approaches. The 20-2-20 Mayo risk model is largely based on disease bulk, while the IMWG model incorporates genetic features; both are easy to apply and distinguish those at highest (50%–60%) and lowest (6%–10%) risk of progression at 2 years.[36] However, there is significant discordance between risk assessment models.[42,43] In a retrospective analysis from two clinical studies incorporating 145 patients, the overall rate of agreement between the Mayo 2008, Mayo 2018 and PETHEMA models was only 16.6% and the ability of the models to classify high-risk versus non-high-risk was significantly different with implications for potential enrolment in therapeutic trials.[42]

Recommendations

- Patients with newly diagnosed SMM should be risk stratified at diagnosis using a validated published model, as a guide to further management. Consider using the Mayo 20-2-20 (2018) and the updated IMWG model 20-2-20 with FISH incorporated (2020). Consider restaging patients with evolving disease. (1C)

SUPPORTIVE CARE

Psychological support

Patient education and psychosocial support are important. The quality-of-life impact of a SMM diagnosis has been examined in a small study[44] that reported multiple symptoms including tiredness, weakness, pain and emotional symptoms such as anxiety and impact on daily life.[44]

Thrombosis risk and prevention

Myeloma is associated with an increased risk of arterial and venous thrombosis with multiple contributing mechanisms identified.[45–52] MGUS studies have demonstrated an increased rate of venous and arterial thrombosis.[53–55] However, there is a lack of confidence as to whether the increased risk of thrombosis relates to the diagnosis of MGUS/SMM itself or any underlying symptoms or conditions which prompt investigations that reveal the diagnosis[56] and no recommendations can be made.

Infection risk and prophylaxis

Infection is a leading cause of death in patients with MM due to a secondary immunodeficiency from the direct effects of myeloma on the immune system,[57–59] end-organ damage[60–62] and treatment itself.[63–65] There is an increased risk of infections in patients with MGUS.[66,67] Vaccination reduces the risk of infection in patients with MM,[68] but the rates of vaccination are suboptimal[57] with impaired responses to vaccination[69–72] and there is often a need for repeated dosing.[73–75] Guidelines exist for the prevention of infection in patients with active MM[68,76] with evidence for infection risk assessment,[77] vaccination,[78] and antimicrobial prophylaxis[79] in reducing infectious complications in patients with MM, but there are no specific guidelines on infection prevention in SMM. Recurrent bacterial infection (>2 in 12 months) was previously a myeloma defining event[80] but was removed in the 2014 revision due to a lack of specificity[9] and would not routinely warrant myeloma-directed therapy. In the absence of specific evidence applicable to SMM, we suggest restaging, and if no evidence of progression to MM, considering prophylactic antibiotics and IV Ig only in patients with recurrent and severe infective episodes based on data from other haematological malignancies and with careful balance of potential risks.

Bisphosphonates

MM-related bone disease results from interaction of malignant myeloma cells with osteocytes, osteoblasts and osteoclasts.[81–84] Bone microarchitectural changes are present in the precursor stages[85] with associated increased fracture

TABLE 3 Risk groups in SMM and their advantages and disadvantages.

Risk score	Risk factors	Risk groups	Risk of progression	Median TTP (months)	Advantages	Disadvantages
PETHEMA (2007)[37]	≥95% atypical plasma cell phenotype by flow (1) Immunoparesis (1)	Low (0 RF) Intermediate (1 RF) High (2 RF)	At 5 years—4% At 5 years—46% At 5 years—72%	NR 73 23	Widespread use in clinical trials of early treatment demonstrating utility	Requires bone marrow biopsy Requires detection of aberrant PC phenotype by multiparameter flow which is not universally available nor used in clinical practice
Mayo (2007)[1]	BMPC <10% and paraprotein >30 g/L BMPC ≥10% and paraprotein ≤30 g/L BMPC ≥10% and paraprotein ≥30 g/L	Low Intermediate High	At 5 years—15% At 5 years—43% At 5 years—69%	228 93 27	Simple to apply if bone marrow performed	Requires bone marrow biopsy Purely reliant on disease bulk
Mayo (2008)[14]	BMPC ≥10% (1) Paraprotein ≥30 g/L (1) Serum free light chain ratio <0.125 or >8 (1)	Low (1 RF) Intermediate (2 RF) High (3 RF)	At 5years—25% At 5 years—51% At 5 years—76%	120 61.2 22.8	Simple to apply if bone marrow performed Widespread use in clinical trials of early treatment demonstrating utility	Requires bone marrow biopsy Requires serum-free light chain measurement Purely reliant on disease bulk
Rajkumar et al (2015)[2]	Risk factors: M-protein ≥30 g/L, IgA paraprotein, immunoparesis (>1 uninvolved Ig), SFLCr <0.125 or >8, eMP 50%–60% clonal BMPCs, MRI with diffuse uptake or 1 lesion, PET-CT bone lesion without osteolysis, presence of t(4;14), del(17p) or gain(1q)	Low (no RF) High (any RF)	—	—	Summarises many demonstrated high-risk features	No weighting to various features and without defined prognostic implication of any one or multiple features Not validated in any cohorts
UAMS[122]	Low-risk GEP4, low paraprotein (<30 g/L) and preserved albumin (≥35 g/L) Low-risk GEP4, high paraprotein (≥30 g/L) or low albumin (<35 g/L) High-risk GEP4	Low Intermediate High	At 2 years—9.4% At 2 years—52% At 2 years—81.8%	—	Incorporates disease biology	Requires bone marrow biopsy Requires genomic data not routinely collected in clinical practice
Mayo (2018) 20-2-20[123]	BMPC >20% (1) Paraprotein >20 g/L (1) Involved: uninvolved SFLC >20 (1)	Low (0 RFs) Intermediate (1 RF) High (≥2 RF)	At 2 years—10% At 2 years—26% At 2 years—47%	109.8 45.1 22.6	Simple to apply if bone marrow performed Well validated Widespread use in clinical trials of early treatment Demonstrated utility of dynamic use	Requires bone marrow biopsy Requires serum-free light chain measurement Purely reliant on disease bulk
CMG[124]	Immunoparesis (1) Paraprotein ≥23 g/L (1) Involved: uninvolved SFLC >30 (1)	Low (0) Low-intermediate (1 RF) Intermediate (2 RF) High (3 RF)	At 2 years—5.3% At 2 years—7.5% At 2 years—44.8% At 2 years—81.3%	—	Does not require bone marrow biopsy	Requires serum-free light chain measurement Purely reliant on disease bulk
IMWG (2020)[36]	BMPC >20% (1) Paraprotein >20 g/L (1) Involved: uninvolved SFLC >20 (1) High-risk cytogenetics [t(4;14), t(14;16), gain(1q), −13 or del(13q)] (1)	Low (0 RF) Low-intermediate (1 RF) Intermediate (2 RF) High (≥3 RF)	At 2 years—6% At 2 years—23% At 2 years—46% At 2 years—63%	—	Incorporates disease biology Demonstrated utility of dynamic use	Requires bone marrow biopsy Requires FISH including some probes which may not be routine (i.e. Ch13)
Dana Farber (2020)[5]	Risk factors: *MYC* alterations, DNA repair pathway alterations, MAPK pathway alterations, t(4;14)	Low (0 RF) High (≥1 RF)	At 2 years—14.4% At 2 years—14.4%	86.4 14.4	Incorporates disease biology	Requires bone marrow biopsy Requires genomic data not routinely collected in clinical practice
PANGEA model[116]	Time varying biomarkers of age, FLC ratio, paraprotein, haemoglobin, creatinine, BMPC, cytogenetics (–17, del(17p), gain(1q), –13, del(13q))	—	—	—	Dynamic model of risk version which does not require bone marrow biopsy Patient-specific probabilities	Recent development and not widely used in therapeutic trials presently

Abbreviations: BMPC, bone marrow plasma cells; CMG, Czech Myeloma Group; GEP, gene expression profiling; IMWG, International Myeloma Working Group; PANGEA, Precursor Asymptomatic Neoplasms by Group Effort Analysis; PETHEMA, Programa Español de Tratamientos en Hematología; RF, risk factor; SFLC(r)—serum-free light chain (ratio); TTP, time to progression; UAMS, University of Arkansas for Medical Sciences.

risk.[86] Bisphosphonates decrease skeletal-related events (SREs) in patients with MM with equivalence between pamidronate and zoledronic acid. A PFS and OS advantage was shown in a network meta-analysis with zoledronic acid but not pamidronate,[87] and bisphosphonates are recommended in all newly diagnosed patients requiring disease treatment regardless of the presence or absence of bone lesions.[88]

Studies in SMM with pamidronate[89,90] and zoledronate[91,92] have shown no impact on median time to progression nor overall survival, but lower rates of SREs at progression in studies compared to placebo. Bisphosphonates are generally well tolerated with documented discontinuation rates of 8%–10% with mainly mild side effects.[93] The rate of serious adverse events studied in patients with osteoporosis is around 1.6%.[94–96]

IMWG guidelines recommend that the presence of osteoporosis should guide bisphosphonate use in SMM with high-risk patients ideally treated as part of a clinical trial.[88] Dual-energy X-ray absorptiometry (DEXA) scanning for bone mineral density may be considered in patients with a diagnosis of osteoporosis[97] to guide bisphosphonate therapy particularly in patients with other risk factors for osteoporosis or features of insufficiency on staging imaging.

Recommendations

- Patients with SMM require clear information and psychological support at the time of their diagnosis and during their follow-up. (1C)
- VTE prophylaxis is not routinely recommended in SMM patients. (1C)
- All patients should be offered vaccination at diagnosis, keep a vaccine logbook and avoid live vaccines (GRADE IV, UK DoH guidance). (1B)
- Vaccination against pneumococcal infections include: Prevenar13 followed 2 months later by Pneumovax23. Functional antibodies should be checked 6 weeks later in those with a history of recurrent or serious infection, to accelerate access to IVIg (UK DoH guidance). Vaccination should be repeated every 5 years. (1B)
- Vaccination against shingles should be offered in patients over 50 years with a two-dose schedule of recombinant zoster vaccine (Shingrix®) 8 weeks to 6 months apart (UK DoH guidance). (1C)
- Patients with recurrent or serious infections should be considered for prophylactic antibiotics. (2C)
- Patients with a low IgG (<4 g/L, residual in case of IgG paraprotein), recurrent or serious infection despite 6 months of prophylactic antibiotics and a documented failure to respond to vaccination should be offered immunoglobulin replacement therapy (NHSE guidance). (2C)
- The annual flu vaccination is recommended for patients and household members. (1C)
- COVID-19 vaccination is recommended in all patients and household members (UK DoH guidance). (1C)
- Routine testing for COVID-19 antibody is currently not recommended. (1C)
- Anti-COVID treatment is recommended for patients who develop COVID-19 infection and are within 5 days of symptom onset. (1C)
- There is a lack of trial data to support the use of bisphosphonates in patients with SMM not requiring anti-myeloma therapy. (1C)

MONITORING OF PATIENTS WITH SMOULDERING MYELOMA

Monitoring in SMM allows the detection of progression with SLiM features prior to the development of CRAB features, reducing frequency of irreversible end-organ damage.[24,98,99] Stratified models of monitoring have been proposed, based on risk of progression, although risk models continue to be refined.[100,101]

Low- and intermediate-risk SMM

For patients with low- or intermediate-risk SMM, regular monitoring is advised.[29,32,102,103] Monitoring should include the assessment of symptoms and the following laboratory tests: full blood count; renal function; bone profile; serum immunoglobulins; serum protein electrophoresis; and serum-free light chain assay.[29] According to guidelines from the European Myeloma Network (EMN) and IMWG, laboratory monitoring should be performed every 2–3 months for the first 6–12 months after diagnosis.[102,103] If results are stable, patients may be followed every 4–6 months for the following year and every 6–12 months thereafter.[102,103] NICE guidelines advise laboratory monitoring every 3 months for the first 5 years after diagnosis,[29] although across the board, guidelines agree that the frequency of laboratory monitoring should be decided based on the long-term stability of the disease.

In the IMWG guidelines, imaging with CT and/or MRI is also recommended annually for the first 5 years, at clinical suspicion/pain or if a progressive increase of M-component is observed.[32,102,103] A detailed imaging algorithm for patients with SMM is reported in the recent IMWG consensus on imaging.[32] Bone disease is a common CRAB feature at progression of SMM and may be asymptomatic.[99,104] Diffusion-weighted MRI is the most sensitive imaging modality for the detection of focal lesions and diffuse infiltration in SMM[35,105,106] and the presence of one focal lesion on MRI may hold prognostic value for progression with bone disease.[98] However, the IMWG serial imaging recommendations are not based on evidence from randomised trials and no assessments of health economic impacts or assessments of capacity have been performed.

High-risk SMM

Evidence-based guidelines are not currently available for the optimal management of high-risk SMM.[107] Definitions

of high-risk SMM differ between trials, making comparisons challenging.[107] Clinicians should use the current 20-2-20 or IMWG risk model, and consider entry into trials for high-risk patients. Early intervention reduces the rates of progression although the effect on mortality is more controversial and all interventions will be associated with some treatment-related toxicity. A meta-analysis of eight RCT comparing early versus deferred treatment in SMM[108] reported that early treatment significantly reduced the progression of SMM (RR = 0.53, 95% CI: 0.33–0.87, $p = 0.01$), particularly in patients considered high risk (RR = 0.51, 95% CI:0.37–0.70, $p = 0.0001$).[108] Treatment of patients with high-risk SMM also significantly reduced mortality (RR = 0.53, 95% CI: 0.29–0.96, $p = 0.04$).[108] Various ongoing trials in high-risk SMM are summarised in Tables 4 and 5, but the two pivotal initial trials using lenalidomide are discussed here. The first trial examining early treatment of SMM was the QuiRedex trial, which randomised 125 patients with high-risk SMM to treatment with lenalidomide and dexamethasone (Rd) or observation and showed longer time to progression and increased 3-year survival in the treatment arm.[109] Longer term follow-up was published in 2016[10] and 2022[110] with a median follow-up of 12.5 (range 10.4–13.6) years the median TTP was 2.1 years in the observation arm versus 9.5 years in the treatment arm (hazard ratio (HR) 0.28, 95%CI 0.18–0.44) with median OS 8.5 years versus not reached in the Rd arm (HR 0.57, 95%CI 0.34–0.95) and with no difference in OS from progression.[110] Despite the overall survival benefit seen in this trial treatment with lenalidomide has not become routine standard of care. Notably, this trial enrolled patients from 2007 to 2010, prior to the IMWG updated diagnostic criteria, and used inadequate imaging (skeletal survey only required in the protocol) to exclude bone disease with associated poor sensitivity. It thus included patients now defined as myeloma, and also raises questions as to the management of the observational arm given the early poor outcomes.

The SWOG E3A06 trial randomised 182 patients with intermediate- or high-risk SMM to treatment with continuous lenalidomide alone or observation between 2013 and 2017, aiming to overcome these limitations, and was reported by Lonial et al. in 2020.[111] At a median of 35-month follow-up, 3-year PFS was 91% vs. 66% ($p = 0.002$) with a HR for in the treatment arm of 0.46 (95% confidence interval 0.08–2.53). Cross-over to lenalidomide prior to formal progression was allowed and will limit any OS data.[112] Importantly, the rate of progression in the observation arm was low (24% in 2 years), perhaps relating to the trial amendment in 2013 allowing patients diagnosed within 5 years rather than solely at diagnosis, suggesting this was not a truly high-risk population. Additionally, grade 3 or 4 adverse events occurred in 41% of patients on lenalidomide and 20% of patients stopped treatment due to adverse effects although there was no significant decline in patient-reported health-related quality of life measures between initiation and 2 years in either group.[111]

Evolving disease

Genomic studies have shown that some patients with SMM (and MGUS) have a similar genetic landscape to MM with a static evolution model; these patients inherently develop the manifestations of MM as tumour burden increases.[5,39,113,114] Thus, for such patients at least, changes in serum biomarkers such as increasing paraprotein and free light chain ratio, and decreasing haemoglobin, may be used to dynamically assess risk.

A retrospective evaluation of the utility of applying the 20-2-20 and IMWG models annually for 5 years post-diagnosis reported that re-stratification led to greater consistency in time to progression between risk categories compared to only using a baseline score.[115] The 2- and 5-year risk of progression from time of assessment remained similar over time although increase in risk group between assessments was prognostic for progression compared with those remaining in the same or lower risk category.[115] The applicability of these risk scores >5 years post-diagnosis has not been studied.

For patients with evolving serological markers, a low threshold should be used for repeat imaging or increasing frequency of follow-up. Several groups have evaluated the value of dynamic markers, with varying definitions of evolving disease (paraprotein rise, decrease in Hb) combined with initial thresholds of paraprotein or BM plasma cell percentage[116–121]; see Table 6.

The PANGEA model used multivariate Cox regression on time-varying biomarkers in a retrospective analysis of 6441 precursor patients (1510 SMM) to develop three models based on availability of bone marrow, blood markers and cytogenetics.[116] The model is available as an online calculator for individual patient risk (www.pangeamodels.org/).[116]

Recommendation

- There is insufficient evidence to treat SMM outside of clinical trials. (1C)
- In low-risk (Mayo (20-2-20)/IMWG) patients, monitor 3 monthly for 1 year and if stable, extend to 6–12 monthly; in intermediate-risk patients, monitor 3 monthly for 1–2 years and if stable, consider extending to 4–6 monthly; in high-risk patients, consider clinical trial entry, otherwise monitor 3 monthly for 5 years. (1C)
- In high-risk patients, consider repeat imaging annually especially if evolving disease markers (1C). Currently, there is a lack of data to support routine re-imaging in all patients without symptoms or clear evidence of progression, but a low threshold should be used for repeat imaging. Patients with equivocal or solitary focal lesions at baseline should have interval imaging (3–6 months). (1C)
- In patients with evolving biochemical markers or increasing Mayo 20-2-20 or IMWG risk group within the first 5 years of diagnosis monitor as high risk. (1C)

TABLE 4 Reported/ongoing phase II/III trials with (interim) reports.

Trial	*n*	Risk stratification	Intervention	Response rates	OS/PFS or TTP
QuiRedex[10,109,110]	119	Paraprotein IgG ≥30 g/L, IgA ≥20 g/L + BMPC ≥10% or one factor with aPC ≥95% and immunoparesis	Lenalidomide + dexamethasone (Rd) versus observation	Induction ORR 79%, ≥CR 14% Maintenance ORR 90%, ≥CR 26%	Median TTP 9.0 versus 2.1 years Median OS NR versus 8.0 years
SWOG E3A06[111]	182	BMPC >10% or sheets of PCs and SFLC ratio <0.125 or >8	Lenalidomide versus observation	ORR 79%, ≥CR 0%	3y PFS 66% vs. 91% ($p = 0.002$)
NCT02697383[125,126]	14	PETHEMA or Mayo (2008) criteria	Ixazomib + dexamethasone (Id)	ORR 57%	At 35 months 35% progression
CENTAURUS[127]	123	BMPC ≥10% to <60% and one of paraprotein IgG ≥30 g/L, IgA ≥20 g/L, or urine M-protein >500 mg/24 h, or SFLC <0.126 or >8 and paraprotein 10–30 g/L or iFLC ≥100 mg/L	Daratumumab—three dose regimens (extended intense, intermediate intense and short dose)	ORR 56%, ≥CR 4.9%	2 years PFS 89.9% vs. 82% vs. 75.3%
NCT02960555[128]	24	Both PETHEMA high-risk criteria	Isatuximab	ORR 62.5%, MRD-ve CR 5%	Ongoing
NCT01331973[129]	31	BMPC ≥10% to <60% and one of paraprotein IgG ≥30 g/L, IgA ≥20 g/L or urine M-protein >500 mg/24 h, or SFLC <0.126 or >8 and paraprotein 10–30 g/L or iFLC ≥100 mg/L	Elotuzumab	ORR 10%	2 years PFS 69%
NCT01484275[130]	85	BMPC ≥10%-<60% and one of paraprotein IgG ≥30 g/L, IgA ≥20 g/L, or urine M-protein >500 mg/24 h, or SFLC <0.126 or >8 and paraprotein 10–30 g/L or iFLC ≥100 mg/L	Siltuximab versus placebo	—	1 year PFS 84.5% vs. 74.4% Median TTP NR versus 23.5 months
NCT01402284[131] Pilot	18	PETHEMA criteria	Carfilzomib, lenalidomide + dexamethasone with lenalidomide maintenance (8xKRd-R)	Post-induction ORR 100%, sCR 55%, MRD-ve MFC 92%, NGS 75%	Estimated 4 years PFS 71% and OS 100%
NCT01572480[132] Phase II	54	PETHEMA, Mayo (2008) or Rajkumar et al. (2015) criteria	8xKRd-R	ORR 100%, ≥CR 75.9%, MRD-ve CR 70.4%	Estimated 8 years PFS 91.2% 8 years OS 100%
NCT02916771[133]	61	Rajkumar et al. (2015) criteria	Ixazomib, lenalidomide + dexamethasone with ixazomib/lenalidomide maintenance (9xIRd-IR)	Post-induction ORR 92.3%, sCR 23.1%	Ongoing
ITHACA[134]	23	Mayo (2018) or PETHEMA criteria	Isatuximab, lenalidomide + dexamethasone (IsaRd)	ORR 100%, ≥CR 30.4%, sCR 13%	Ongoing
ASCENT[135]	87	Mayo (2018) or ASCENT score	Daratumumab, carfilzomib, lenalidomide + dexamethasone (Induction C1–6, consolidation C7–12, maintenance C13–24)	Best ORR 97%, ≥CR 63%, sCR37%, 84% MRD-ve (61% CR MRD-ve)	3 years PFS 89.9%
GEM-CESAR[136]	90	Both BMPC ≥10% and paraprotein ≥30 g/L or one of these and PETHEMA high risk	6xKRd + melphalan ASCT + 2xKRd + maintenance Rd	Post consolidation ≥CR 72%, MRD-ve 68%	5 years PFS 94% and OS 95%
NCT02603887[137]	12	Mayo (2008), PETHEMA or UAMS criteria	Pembrolizumab	ORR 7.6%, sustained MRD-ve CR in the one responder	—
NCT01718899[71]	20	Mayo (2008)	PVX-410 vaccine ± lenalidomide	Immunogenicity in 95% monotherapy and 100% in combination	—

Abbreviations: aPC, atypical plasma cells; BMPC, bone marrow plasma cell; iFLC, involved free light chain; MFC, multiparameter flow cytometry; MRD, minimal residual disease; NGS, next-generation sequencing; NR, not reached; ORR, overall response rate; PCs, plasma cell; PFS, progression-free survival; (s)CR, (stringent) complete response; SFLC, serum-free light chains; TTP, time to progression.

TABLE 5 Ongoing and planned phase II/III trials.

Trial	Phase	Intervention
NCT02916771	II	IRd
AQUILA	III	Daratumumab versus observation
ITHACA	III	IsaRd
E-PRISM	II	EloRd
NCT04776395	II	Iberdomide + dexamethasone versus iberdomide
HO147SMM	III	KRd versus. Rd
EAA173/DETER-SMM	III	DRd versus Rd
B-PRISM	II	DVRd
ASCENT	II	DKRd
GEM-CESAR	II	KRd + ASCT+KRd-R
ImmunoPRISM	II	Teclistamab, lenalidomide, dexamethasone
CAR-PRISM	II	Anti-BCMA CAR T cells
NCT02886065	II	PVX-410 + citarinostat ± lenalidomide
MODIFY	II	Isatuximab/Iberdomide/Dexamethasone

TABLE 6 Evolving disease models.

Evolving criteria	Prognostic implication	Reference
Increase in paraprotein at each of first two consecutive follow-up visits	Median TTP 1.3 years versus 3.9 years if stable	117
Paraprotein increase of ≥10% in 12 m from baseline ≥30 g/L or in 36 m from baseline <30 g/L	HR for progression 5.1 (3.4–7.6) Median TTP from recognition of 'evolving' 1.1 years versus 3.8 years	118
eMP (paraprotein increase ≥10% in 6 m from baseline ≥30 g/L or ≥25% in 12 m regardless of baseline) eHb (haemoglobin decrease ≥5 g/L from baseline in 12 m)[a]	eMP OR for progression in 2 years 8.2 (3.19–21.05), 2 years progression 63.8% eHb OR for progression in 2 years 5.86 (2.13–16.2), 2 years progression 64.6% wMP + eHb 2 years progression 81.5% (and +BMPC >20% 90.5%)	119
Group-based trajectory modelling: eMP (median 64% increase), eHb (median 15.7 g/L decrease), eFLCr (median 169% increase) prognostic	eMP median TTP 40 m, 2 years progression 36% eHb median TTP 26 m, 2 years progression 43% eFLCr median TTP 45 m, 2 years progression 30%	120
PANGEA model incorporating age, FLCr, paraprotein, creatinine, haemoglobin (and BMPC%, and cytogenetics (gain(1q), del(17p), monosomy 13))	Individualised progression risk Available at www.pangeamodels.org/	116

Abbreviations: BMPC, bone marrow plasma cells; eHb, evolving haemoglobin; eFLCr, evolving free light chain ratio; eMP, evolving monoclonal protein; TTP, time to progression.

[a]Not validated in Ref. [121].

- Consider stratified clinical models for long-term monitoring, in either the primary or secondary care settings using healthcare professionals (nurses, primary care, laboratory staff). All the models need to be adequately resourced and overseen by well-trained and motivated staff to be successful. (1A)

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CONFLICT OF INTEREST STATEMENT

All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request.

REVIEW PROCESS

The members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant task force and the literature search will be re-run every 3 years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk/guidelines).

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