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N Engl J Med, 379, 2517–28. Zent CS, Burack WR (2014). Mutations in chronic lymphocytic leukemia and how they affect therapy choice: focus on NOTCH1, SF3B1, and TP53. Hematology Am Soc Hematol Educ Program, 2014, 119–24. Zent CS, et al. (2008). The prognostic significance of

cytopenia in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL). Br J Haematol, 141, 615–21. 22.4.6 Plasma cell myeloma and related monoclonal gammopathies S. Vincent Rajkumar and Robert A. Kyle ESSENTIALS The monoclonal gammopathies, also referred to as paraproteinaemias, are a group of neoplastic (or potentially neoplastic) diseases associ- ated with the proliferation of a single clone of immunoglobulin-se- creting plasma cells. Monoclonal gammopathy of undetermined significance (MGUS) MGUS is an asymptomatic clonal plasma cell disorder characterized by a serum monoclonal (M)-protein level less than 30 g/litre, less than 10% of monoclonal bone marrow plasma cells, and no evi- dence of hypercalcaemia, renal insufficiency, anaemia, or bone le- sions (CRAB) related to the plasma cell proliferative process, and no evidence of any other myeloma-defining events (MDEs). Epidemiology and prognosis—MGUS is found in 3% of people aged over 50 years and in 5% of those over 70 years. The risk of progres- sion to plasma cell myeloma or a related disorder is about 1% per year, with factors increasing the risk being higher concentration of the monoclonal protein, some particular types of monoclonal pro- tein (IgA and IgM > IgG), or an abnormal serum free light-chain ratio. Management—observation is the standard of care. The mono- clonal protein in the serum and urine is monitored, together with re-evaluation of clinical and laboratory tests, to determine whether myeloma or a related disorder has developed. Plasma cell myeloma Plasma cell myeloma (commonly referred to as multiple myeloma) is a clonal plasma cell malignancy that accounts for about 10% of haematological cancers. The cause is unknown. Fluorescence in situ hybridization of bone marrow plasma cells reveals specific primary translocations or trisomies in more than 90% of patients. The pres- ence of del 17p, t(4;14), t(14;16), and t(14;20) occur in 20 to 25% of patients, and indicate higher-risk disease. Clinical features—myeloma is defined by the presence of 10% or more clonal plasma cells in the bone marrow (or a biopsy-proven plasmacytoma) plus any one or more MDEs: CRAB features attrib- utable to the plasma cell disorder, 60% or more clonal plasma cells in the bone marrow, serum free light-chain ratio of at least 100 (pro- vided involved free light-chain level is ≥100 mg/litre), and/or more than one focal lesion on magnetic resonance imaging. The most common symptoms are weakness, fatigue, and bone pain. Investigations—an M-protein (paraprotein) is found in the serum or urine at diagnosis in 97% of cases. The bone marrow usually con- tains more than 10% clonal plasma cells. Monoclonal plasma cells in myeloma and related monoclonal gammopathies are light-chain restricted to either κ or λ expression in their cytoplasm. This mono-typic pattern can be identified on flow cytometry and is critical for differentiating monoclonal from reactive (polyclonal) plasmacytosis. Conventional radiographs show lytic lesions, osteoporosis, or frac- tures in almost 80% of patients at diagnosis. Treatment and prognosis—first-line options, aside from supportive care, are (1) initial therapy with a triplet regimen such as bortezomib, lenalidomide, and dexamethasone (VRD); (2) autologous stem cell transplantation (ASCT) in eligible patients; and (3) consideration of maintenance therapy with lenalidomide. With this approach, pa- tients can stay in remission for approximately 3 to 4 years. At relapse, therapy includes newer agents such as carfilzomib, pomalidomide, ixazomib, daratumumab, and elotuzumab, administered usually in two- or three-drug combinations. The choice of therapy at relapse is usually dictated by aggressiveness of the relapse, and drug avail- ability. The median survival of myeloma is about 6 to 7 years. Waldenström’s macroglobulinaemia Waldenström’s macroglobulinaemia (WM) is characterized by the presence of an IgM M-protein, 10% or more lymphoplasmacytic infiltration of the bone marrow, and symptoms such as anaemia, lymphadenopathy, and hyperviscosity. Rituximab, a monoclonal antibody directed against CD20, is used as initial therapy in conjunc- tion with other active drugs. Ibrutinib is a new agent that is highly active against WM. The median survival is longer than 5 years. Immunoglobulin light-chain

amyloidosis Immunoglobulin light-chain (AL) amyloidosis (formerly referred to as primary amyloidosis) is a clonal plasma cell disorder character- ized by tissue deposition of fibrils consisting of monoclonal κ or λ light chains. Weakness, fatigue, and weight loss are the commonest

22.4.6 Plasma cell myeloma and related monoclonal gammopathies 5311 initial symptoms. Characteristic findings include periorbital purpura (15% of cases), macroglossia (10%), nephrotic syndrome/renal failure (25%), and congestive heart failure (20%), but virtually any organ system can be affected. Standard treatment is with bortezomib, cyclophosphamide, dexa- methasone (VCD), and ASCT in selected patients. Prognosis varies greatly depending on the presence and extent of organ involvement. Other conditions Other less common monoclonal gammopathies include smoul- dering multiple myeloma; plasma cell leukaemia; POEMS syndrome— characterized by polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; solitary plasmacytoma; and heavy- chain diseases. Introduction The monoclonal gammopathies, also referred to as paraprotein aemias, are a group of clonal plasma cell disorders associated with the proliferation of a single clone of immunoglobulin-secreting plasma cells. They include monoclonal gammopathy of undeter- mined significance (MGUS); plasma cell myeloma (commonly referred to as multiple myeloma); smouldering myeloma (SM); Waldenström's macroglobulinaemia (WM); heavy-chain diseases; solitary plasmacytoma of bone, extramedullary plasmacytoma, plasma-cell leukaemia, POEMS syndrome; and immunoglobulin light-chain (AL) amyloidosis. The disease definition for the major plasma cell disorders is given in Table 22.4.6.1. Monoclonal gammopathies are characterized by the secretion of electrophoretically and immunologically homogeneous monoclonal (M)-proteins. Each M-protein consists of two heavy (H) polypep- tide chains of the same class and subclass and two light (L) poly- peptide chains of the same type. The heavy polypeptide chains are designated by Greek letters: γ in IgG, α in IgA, μ in IgM, δ in IgD, and ε in IgE. The light-chain types are κ (kappa) or λ (lambda). Recognition of M-proteins Agarose gel electrophoresis is preferred for the detection of M- proteins. Immunofixation is necessary to confirm the presence of an M-protein and distinguish the immunoglobulin class and its light-chain type. Serum protein electrophoresis should be performed when mye- loma, WM, or AL amyloidosis is suspected. An M-protein is charac- terized by a narrow peak or spike in the densitometer tracing, or as a dense, discrete band on agarose gel (Fig. 22.4.6.1). In contrast, an excess of polyclonal immunoglobulins (having one or more heavy- chain types and both κ and λ light chains) produces a broad-based peak or broad band. It is important to differentiate an M-protein from a polyclonal increase because the former is associated with a malignant process or a potentially neoplastic condition, whereas a polyclonal increase in immunoglobulins is associated with a reactive or inflammatory process. Serum protein immunofixation is the pre- ferred technique for identifying the heavy- and light-chain type of the M-protein, and in detecting small M-proteins that may not be apparent on electrophoresis. In myeloma and related disorders, free (unbound) monoclonal immunoglobulin light chains may be se- creted in addition to intact immunoglobulin M-proteins. Less fre- quently, free monoclonal immunoglobulin light chains are secreted without any evidence of an intact immunoglobulin or heavy-chain component. These free light chains (FLCs) can be missed on serum electrophoresis and immunofixation. They are detected by the serum FLC assay or by electrophoresis and immunofixation of an adequately concentrated 24-h urine specimen. The serum FLC assay measures free κ and λ light chains; an abnormal serum FLC ratio of κ to λ light chains is indicative of a monoclonal process. Diseases associated with an M-protein in the serum and/or urine, as found recently in the authors' practice, are shown in Fig. 22.4.6.2. Monoclonal gammopathy of undetermined significance The term 'monoclonal gammopathy of undetermined

significance’ (MGUS) denotes the presence of an M-protein in persons without evidence of myeloma, WM, AL, or related disorders. MGUS is characterized by a serum paraprotein concentration of less than 30 g/litre, fewer than 10% plasma cells in the bone marrow, and no evidence of end-organ damage (hypercalcaemia, renal insuffi- ciency, anaemia, or bone lesions (‘CRAB’)) related to the plasma cell proliferative process or other myeloma-defining events (MDEs) (Table 22.4.6.1). The prevalence of MGUS is 3% in patients aged 50 years or older, 5% in those over 70 years of age, and is higher in men than women (Fig. 22.4.6.3). The prevalence of MGUS is twice as high in black patients compared with white patients. Clinical course of MGUS MGUS is detected incidentally during clinical workup of a variety of symptoms and laboratory abnormalities. In a series of 241 patients with MGUS seen at Mayo Clinic from 1956 to 1970 and followed for up to 39 years, 27% developed myeloma, WM, or a related disorder. The actuarial rate of progression to one of these disorders was 17% at 10 years, 34% at 20 years, and 39% at 25 years, a rate of approximately 1.5% per year. A separate population-based study of 1384 patients with MGUS from the 11 counties of southeastern Minnesota con- firmed the clinical course of MGUS that was described in the original Mayo Clinic referral population. The M-protein was of the IgG type in 70%, IgM in 15%, IgA in 12%, and biclonal in 3%. After 11 009 person-years (median 15.4 years; range 0–35 years) of follow-up, 115 patients (8%) developed multiple myeloma, AL, WM, plasmacytoma, chronic lymphocytic leukaemia, or related plasma cell disorders. The rate of progression was 10% at 10 years, 21% at 20 years, and 26% at 25 years, which is approximately 1% per year (Fig. 22.4.6.4). Differential diagnosis of MGUS from multiple myeloma and related disorders MGUS is differentiated from myeloma and related disorders using the criteria listed in Table 22.4.6.1. Thus the presence or absence of MDEs is critical to distinguish MGUS from myeloma. MGUS is differentiated from SM based on the level of the M-protein and the extent of bone marrow involvement. No single test will distinguish

 the patient with MGUS who remains stable from those who may eventually develop myeloma or related disorders. Thus most pa- tients need to be observed indefinitely. The paraprotein level in the serum and urine should be serially measured, along with periodic re-evaluation of clinical and other features to determine whether myeloma or a similar disorder is present. The cytogenetic changes detected by fluorescence in situ hybridization (FISH) in MGUS are similar to those seen in multiple myeloma. Although the main concern with MGUS is the risk of progression to a malignancy such as myeloma or WM, there are other disorders that are associated with an M-protein that should be considered. These include membranoproliferative glomerulonephritis, periph- eral neuropathy, and certain skin diseases, among others. Risk stratification and management Patients with MGUS do not require therapy. The serum FLC assay is of prognostic value in MGUS. Patients with an abnormal FLC ratio (<0.26 or >1.65) have an approximately threefold higher risk of progression. Other risk factors for progression of MGUS include the size of the M-protein, and the type of M-protein. Patients with serum M-protein levels less than 15 g/litre, IgG class, and normal FLC ratio are considered as low-risk MGUS (2% lifetime risk of Table 22.4.6.1 International Myeloma Working Group diagnostic criteria for plasma cell myeloma and related plasma cell disorders Disorder Disease definition Non-IgM monoclonal gammopathy of undetermined significance (MGUS) All 3 criteria must be met: Serum monoclonal protein (non-IgM type) <30 g/litre Clonal bone marrow plasma cells <10%a Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder Smouldering myeloma Both criteria must be met: Serum monoclonal protein (IgG or IgA) ≥30 g/litre, or urinary

monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60% Absence of myeloma defining events or amyloidosis Plasma cell myeloma Both criteria must be met: Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma Any one or more of the following myeloma defining events: Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: Hypercalcaemia: serum calcium >0.25 mmol/litre (>1 mg/dl) higher than the upper limit of normal or >2.75 mmol/litre (>11 mg/dl) Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 µmol/litre (>2 mg/dl) Anaemia: haemoglobin value of >20 g/litre below the lower limit of normal, or a haemoglobin value <100 g/litre Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT) Clonal bone marrow plasma cell percentage ≥60% Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved FLC level must be ≥100 mg/litre)

> 1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5 mm in size) IgM monoclonal gammopathy of undetermined significance (IgM MGUS) All 3 criteria must be met: Serum IgM monoclonal protein <30 g/litre Bone marrow lymphoplasmacytic infiltration <10% No evidence of anaemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder. Light-chain MGUS All criteria must be met: Abnormal FLC ratio (<0.26 or >1.65) Increased level of the appropriate involved light chain (increased kappa FLC in patients with ratio >1.65 and increased lambda FLC in patients with ratio <0.26) No immunoglobulin heavy-chain expression on immunofixation Absence of end-organ damage that can be attributed to the plasma cell proliferative disorder Clonal bone marrow plasma cells <10% Urinary monoclonal protein <500 mg/24 h Solitary plasmacytoma All 4 criteria must be met: Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Normal bone marrow with no evidence of clonal plasma cells Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder Solitary plasmacytoma with minimal marrow involvementb All 4 criteria must be met: Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Clonal bone marrow plasma cells <10% Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder a A bone marrow can be deferred in patients with low-risk MGUS (IgG type, M-protein level <15 g/litre, normal free light chain ratio) in whom there are no clinical features concerning for myeloma. b Solitary plasmacytoma with 10% or more clonal plasma cells is considered as plasma cell myeloma. Reprinted from The Lancet, Vol 15, Rajkumar SV et al., International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma, Pages e538–48, Copyright © 2014, with permission from

> Elsevier.

22.4.6 Plasma cell myeloma and related monoclonal gammopathies 5313 progression) (Table 22.4.6.2). In these patients, if the diagnosis of MGUS is suspected and there is no concern for malignancy, baseline bone marrow examination and skeletal radiography can be omitted. They can be reassessed in 6 months, and if stable, further workup is needed only if symptoms suspicious of myeloma or a related dis- order develop. Patients with any one or more risk factors (e.g. M- protein level ≥15 g/litre, non-IgG class, or abnormal FLC ratio) need a baseline bone marrow examination, and skeletal radiographs (or similar bone examination). Such patients need to be reassessed in 6 months, and if stable, yearly thereafter. Biclonal gammopathies Occasionally, patients are found to have two M-proteins (biclonal gammopathies). Most such patients have biclonal gammopathy of undetermined significance, with the remainder representing plasma cell myeloma, WM, or another malignant lymphoproliferative dis- order. Triclonal gammopathies may also occur. Light-chain MGUS Approximately 1% of the general population over the age of 50 has a light-chain MGUS characterized by an abnormal serum FLC ratio without any evidence of intact immunoglobulin heavy-chain (IgH) expression (Table 22.4.6.1). These patients are observed and may remain stable for many years. Smouldering (asymptomatic) myeloma SM is an intermediate clinical stage between MGUS and plasma cell myeloma. SM is characterized by a serum monoclonal protein level of 30 g/litre or more, a urine M-protein concentration of 500 mg/24 h or more, and/or a level of bone marrow clonal plasma cells of 10 to 60%, and no MDEs (Table 22.4.6.1). The subset of SM patients without an intact immunoglobulin, but with light-chain only presentation are considered to have light-chain SM. In contrast to MGUS, the risk of progression of SM to plasma cell myeloma or AL is much higher at almost 10% per year for the first 5 years, approxi- mately 3% per year for the next 5 years, and then 1 to 2% per year for the following 10 years. Thus patients with SM need to be monitored more closely, every 3 to 4 months. Selected patients with SM who are considered to have high-risk features (Table 22.4.6.3) may be candi- dates for clinical trials testing preventive strategies. Plasma cell myeloma Plasma cell myeloma (multiple myeloma, myelomatosis) is a plasma cell malignancy that commonly presents with osteolytic skeletal de- struction, renal failure, anaemia, recurrent bacterial infections, or hyperviscosity syndrome. History Myeloma was documented by the description of Sarah Newbury which was followed by that of Thomas Alexander McBean a few years later. The physician and clinical pathologist, Henry Bence (a) (b) alb γ
Fig. 22.4.6.1 (a) Monoclonal pattern of serum protein as traced by a densitometer after electrophoresis on agarose gel; tall, narrow-based peak of γ mobility. (b) Monoclonal pattern from electrophoresis of serum on agarose gel (anode on left); dense, localized band representing monoclonal protein of γ mobility. From Kyle RA, Katzmann JA (1997). Immunochemical characterization of immunoglobulins. In: Rose NR, et al. (eds) Manual of clinical laboratory immunology, 5th edition, pp. 156–76. ASM Press, Washington, DC. By permission of the American Society for Microbiology. Monoclonal gammopathies Mayo Clinic 1960–2013 n = 48 853 SMM 4% (1908) Solitary or extramedullary 2% (902) Macro 3.0% (1322) Other 4% (2187) MGUS 57% (27 884) Lymphoproliferative 3% (1434) (a) AL amyloidosis 9% (4593) Plasma cell myeloma 18% (8619) Monoclonal gammopathies Mayo Clinic 2013 n = 1773 Smouldering myeloma 2.5% (45) Solitary or extramedullary 0.5% (12) Macro 4.5% (84) Other 6% (101) MGUS 56% (992) Lymphoproliferative 1.5% (30) (b) AL amyloidosis 9% (159) Plasma cell myeloma 20% (350)
Fig. 22.4.6.2 Types of monoclonal gammopathies at the Mayo Clinic (a) 1960–2013 and (b) 2013.

SMM, smouldering multiple myeloma.

section 22 Haematological disorders 5314 Jones described the unusual protein excreted by McBean in the mid 19th century. The term ‘multiple myeloma’ was introduced by J. Von Rustizky in 1873. It was the case report of Dr Loos, published by Professor Otto Kahler in 1889, that introduced multiple myeloma to clinical practice. This has now been replaced by the World Health Organization’s favoured term, plasma cell myeloma. The introduction of melphalan in the late 1950s was a major step forward in the treatment of myeloma. Autologous stem cell transplantation (ASCT) was introduced in the 1980s and refined in the 1990s. Later, thalidomide, bortezomib, and lenalidomide be- came important agents for treatment of myeloma. More recently, a number of new treatments have emerged that greatly prolong the survival of the disease. Epidemiology and aetiology Myeloma accounts for 1% of all malignant diseases and slightly more than 10% of haematological malignancies in the United States of America. The annual incidence is 4 to 5 per 100 000/year. The apparent increase in the incidence of myeloma during the past few decades is probably related to the increased availability and use of medical facil- ities, especially in older persons. The incidence in African Americans is twice that in white populations, but rates are lower in Asian popu- lations. The median age at diagnosis is 65 to 70 years. Only 10% of patients are younger than 50 years, and 2% are younger than 40 years. The cause of myeloma is unknown, but radiation, benzene and other organic solvents, herbicides, and insecticides may play a role. The dis- ease is a rare complication of Gaucher disease (see Chapter 12.8); poly- clonal gammopathy is frequent in the untreated disease and MGUS appears to occur at greater frequency than in age-matched control subjects. Myeloma has been reported in two or more first-degree rela- tives and in identical twins, suggesting a genetic element. Biological aspects Myeloma evolves from the premalignant stage of MGUS. The pre- cise mechanisms of disease evolution are unclear, but the two key steps are establishment of the premalignant clone (MGUS), and the progression of MGUS to malignancy (myeloma). The development of primary IgH translocations (40%), trisomies (40%), or a com- bination of IgH translocations and trisomies (15%) are critical in the pathogenesis of MGUS. The five most common primary IgH translocations involve the IgH locus on chromosome 14q32, one of five recurrent partner chromosome loci: 11q13 (CCND1 (cyclin D1 gene)), 4p16.3 (FGFR-3 and MMSET), 6p21 (CCND3 (cyclin D3 gene)), 16q23 (c-MAF), and 20q11 (MAFB). The progression of MGUS to multiple myeloma is associated with secondary cytogen- etic events, RAS mutations, overproduction of interleukin (IL)-6, IL-1β, macrophage inflammatory protein-α (MIP-1α), and tumour necrosis factor-α (TNFα). Clinical manifestations Bone pain, frequently in the back or chest, is present at diagnosis in almost two-thirds of patients. This is secondary to osteolytic bone lesions that are a prominent feature of most patients with myeloma. Loss of height from multiple vertebral collapses may occur. Other common symptoms of multiple myeloma include weakness and fatigue, which are often due to anaemia. Anaemia is the result of bone marrow infiltration by clonal plasma cells. Renal failure is present in approximately 20% of patients at diagnosis. The two major causes of renal failure are light-chain cast nephropathy and hypercalcaemia. Light-chain cast nephropathy occurs in patients with high levels of circulating FLC (typically >500 mg/litre) and is characterized by the presence of dense, waxy, laminated casts in the distal and collecting tubules. The casts consist mainly of monoclonal light chains. Dilatation and atrophy of the tubules occur, and the entire nephron becomes nonfunctional. Hypercalcaemia, present in 15% of patients initially, is a major and treatable cause of renal insufficiency. Other causes of renal dysfunction are dehydration, concurrent amyl- oidosis, and hyperuricaemia. Extramedullary plasmacytomas are un-common and are usually observed late in the course of the disease as large, purplish,

subcutaneous masses. Other manifestations of myeloma include increased suscepti- bility to infections. The incidence of bacterial infection is increased. Impairment of antibody response, neutropenia, treatment with 8 6 4 2 0 10 50 60 Age (years) Prevalence (%) Females Males 70 80 90 Fig. 22.4.6.3 Prevalence of MGUS according to age. The I-bars represent 95% confidence intervals. Years of age greater than 90 have been collapsed to 90 years of age. From Kyle RA (2006). Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med, 354, 1362–9. Copyright © 2006 Massachusetts Medical Society. Reprinted with permission. Progression Cumulative probability (%) Years n = 1384 Pt at risk (no.) 30 21% 26% 10% 25 20 15 10 5 0 0 1384 867 423 177 56 17 5 10 15 20 25 Fig. 22.4.6.4 Probability of progression among 1384 residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance (MGUS) was diagnosed, 1960–1994. The curve shows the probability of progression of MGUS to plasma cell myeloma, IgM lymphoma, primary amyloidosis, macroglobulinaemia, chronic lymphocytic leukaemia, or plasmacytoma (115 patients). The bars show 95% confidence intervals. From Kyle RA (2002). Prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med, 346, 564–9. Copyright © 2002 Massachusetts Medical Society. Reprinted with permission.

 glucocorticoids, and reduction of normal immunoglobulins in- crease the likelihood of infection. Organomegaly is uncommon; the liver is palpable in about 5% of patients, and the spleen in 1%. Radiculopathy is the most frequent neurological complication re- sulting from bone disease in the spine, and usually involves the thoracic or lumbosacral areas. Compression of the spinal cord from extradural myeloma occurs in 5% of patients. Leptomeningeal in- volvement is uncommon but is being recognized more frequently. Laboratory findings If myeloma is suspected, the laboratory tests listed in Box 22.4.6.1 should be performed. Anaemia is initially present in 70% of patients but eventually is found in almost all. The serum protein electrophor- etic pattern shows a spike or localized band in 80% of cases; serum immunofixation increases the sensitivity to 93%. Addition of the serum FLC assay and/or 24-h urine studies will detect an M-protein in 97 to 98% of patients with myeloma. Approximately 2% of pa- tients with myeloma do not secrete any M-protein (nonsecretory multiple myeloma). The M-protein type is IgG in about 50% of pa- tients, IgA in 20%, FLC only in 15 to 20%, IgD in 2%, and biclonal in 2%. Hypercalcaemia is initially present in almost 15%; about one- fifth have renal failure at diagnosis. The bone marrow contains 10% or more plasma cells in 97% of patients; the remaining patients must have evidence of a biopsy- proven plasmacytoma elsewhere to meet the criteria for myeloma (Table 22.4.6.1). Monoclonal plasma cells in myeloma and related monoclonal gammopathies are light-chain restricted to either κ or λ (but not both) expression in their cytoplasm. This monotypic pat- tern can be identified on flow cytometry and is critical for differen- tiating monoclonal from reactive (polyclonal) plasmacytosis that can occur due to connective tissue disorders, metastatic carcinoma, liver disease, or chronic infections, etc. Bone marrow samples must be tested using FISH or similar methods for the presence of IgH translocations, trisomies, deletion 17p, and gain 1q, all of which help with prognostic assessment. Radiography Conventional radiographs show abnormalities consisting of lytic le- sions, osteoporosis, or fractures in almost 80% of patients at diag- nosis. The vertebrae, skull, thoracic cage, pelvis, and humeri and femora are the most commonly involved sites. Bone disease can be Table 22.4.6.2 Risk of progression of monoclonal gammopathy of undetermined significance to myeloma or related disorders Risk group Relative risk of progression Cumulative absolute risk of progression at 20 years (%)a Cumulative absolute risk of progression at 20 years accounting for death as a competing risk (%)b Low risk: serum M-protein level <15 g/litre, IgG

subtype, normal free light chain ratio (0.26-1.65) 1 5 2 Low-intermediate risk: any 1 factor abnormal 5.4 21 10 High-intermediate risk: any 2 factors abnormal 10.1 37 18 High risk: all 3 factors abnormal 20.8 58 27 a Estimates in this column represent the risk of progression assuming that patients do not die of other causes during this period. b Estimates in this column represent the risk of progression calculated by using a model that accounts for the fact that patients can die of unrelated causes during this time. Ig, immunoglobulin. Adapted from Rajkumar SV, et al. (2005). Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance (MGUS). Blood, 106, 812–817. © The American Society of Hematology. Table 22.4.6.3 Criteria for high-risk smouldering myeloma Patients who meet the International Myeloma Working Group Criteria for Smouldering Myeloma who have bone marrow clonal plasma cells ≥10% and any one or more of the following: Serum M-protein level ≥30g/litre IgA SM Immunoparesis with reduction of two uninvolved immunoglobulin isotypes Serum involved/uninvolved free light chain ratio ≥8 (but less than 100) Progressive increase in M-protein level (evolving type of SM)a Bone marrow clonal plasma cells 50–60% Abnormal plasma cell immunophenotype (≥95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes t (4;14) or del 17p or 1q gain Increased circulating plasma cells MRI with diffuse abnormalities or 1 focal lesion PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction M, monoclonal; MRI, magnetic resonance imaging; PET-CT, positron emission tomography computed tomography; SM, smouldering myeloma. a Increase in serum monoclonal protein by ≥25% on two successive evaluations within a 6-month period Reproduced from Rajkumar SV, et al. (2005). Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance (MGUS). Blood, 106, 812–817. © The American Society of Hematology. Box 22.4.6.1 Baseline tests for patients in whom plasma cell myeloma is suspected • Complete blood count, creatinine, calcium • Serum protein electrophoresis, immunofixation, quantitation of im- munoglobulins and serum FLCs • Serum albumin, β2-microglobulin, C-reactive protein, and lactate dehydrogenase • 24-h urine electrophoresis and immunofixation • Bone marrow aspiration, biopsy, with FISH studies to detect chromosome 14q32 translocations, trisomies, deletion 17p, and amplification 1q • Metastatic bone survey, including single views of humeri and femurs; or preferably low-dose whole-body CT scan, or PET-CT scan • Peripheral blood circulating plasma cells by flow cytometry

 detected in a more sensitive manner by low-dose whole-body com- puted tomography (CT) scanning, or positron emission tomog- raphy (PET)-CT scanning. Magnetic resonance imaging (MRI) is useful in patients with suspected SM, where the finding of multiple focal lesions will upstage the diagnosis to overt plasma cell mye- loma. MRI scans are also useful in patients with suspected spinal cord involvement. Diagnosis The diagnosis of myeloma requires the presence of 10% or more clonal plasma cells in the bone marrow (or a biopsy-proven plasmacytoma) plus any one or more MDEs: CRAB features attrib- utable to the plasma cell disorder, 60% or more clonal plasma cells in the bone marrow, serum FLC ratio of at least 100 (provided in- volved FLC level is ≥100 mg/litre), and/or more than one focal le- sion on MRI. Plasma cell myeloma needs to be differentiated from related plasma cell disorders based on the diagnostic criteria listed in Table 22.4.6.1. Prognostic features The median duration of survival in myeloma is approximately 6 to 7 years, but there is considerable variability from one patient to an- other. The prognosis is affected by the presence or absence of certain cytogenetic abnormalities. Patients with trisomies, t(11;14) or t(6;14) are considered to have standard risk myeloma. The presence of del 17p, t(4;14), t(14;16), and t(14;20) is associated with adverse prog- nosis and is considered as

high risk. Other simple markers such as serum albumin, lactate dehydrogenase, and serum β2 microglobulin levels also affect prognosis. These are incorporated into the Revised International Staging System (RISS) (Table 22.4.6.4). In addition, other markers of adverse prognosis include the presence of renal failure, increased circulating plasma cells, high plasma cell prolifera- tive rate, and extramedullary disease. Treatment of newly diagnosed plasma cell myeloma Patients with myeloma require therapy. The specific steps of therapy include initial therapy, stem cell transplantation (if eligible), consoli- dation/maintenance therapy, and treatment of relapse. Patients must be evaluated carefully to ensure that they meet criteria for myeloma, and that they do not have MGUS or SM. The specific regimens used in therapy vary depending on the availability of new drugs. The field is advancing rapidly, and several new drugs are in development. Improved treatment options have greatly improved the outcome in myeloma. The most common regimens used in the treatment of myeloma are listed in Table 22.4.6.5. Patients eligible for autologous stem cell transplantation Transplant eligible patients (typically patients less than 65–70 years with good performance status) receive approximately four cycles of initial therapy followed by stem cell collection and ASCT. Selected patients with standard risk myeloma who respond well to induction can opt for delayed ASCT; in this strategy, stem cells are collected after four cycles of initial therapy and cryopreserved for future use (Fig. 22.4.6.1). If patients are considered eligible for ASCT, it is im- portant to avoid melphalan which can damage the stem cells. ASCT is not curative in myeloma, but prolongs overall survival (OS). ASCT is safe, with a treatment-related mortality of less than 1% if patients are appropriately selected. The initial therapy for transplant eligible patients typically con- sists of a triplet regimen. We prefer bortezomib, lenalidomide, plus dexamethasone (VRD) which is associated with a high response rate. In a recent randomized trial conducted by the Southwest Oncology Group (SWOG), progression-free survival (PFS) and OS were sig- nificantly superior with VRD compared with lenalidomide plus dexamethasone (Rd). Other alternative regimens are bortezomib, thalidomide, dexamethasone (VTD), and bortezomib, cyclophos- phamide, and dexamethasone (VCD). With all these regimens, we prefer the low-dose dexamethasone regimen (40 mg once a week) to minimize toxicity. In a randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG), the low-dose dexametha- sone approach was associated with superior OS and significantly lower toxicity compared to the high-dose pulsed dexamethasone schedules. We also prefer the once-weekly subcutaneous schedule of bortezomib in all regimens. This approach greatly reduces the risk of neurotoxicity. Higher doses of dexamethasone, and twice-weekly bortezomib can be considered if a rapid response is desired such as patients with acute kidney injury due to cast nephropathy, extensive extramedullary disease, plasma cell leukaemia, or impending cord compression. Deep venous thrombosis occurs in approximately 15% of patients given thalidomide or lenalidomide and so prophylaxis with aspirin or warfarin or low-dose heparin is needed in all patients receiving these drugs. Table 22.4.6.4 Revised International Staging System for plasma cell myeloma Stage Frequency (% of patients) 5-year survival rate (%) Stage 1 ISS stage I (serum albumin >35 g/L, serum beta-2-microglobulin <3.5 mg/L) and No high-risk cytogenetics Normal LDH 28 82 Stage II Neither stage I or III 62 62 Stage III ISS stage III (serum beta-2-microglobulin >5.5 mg/L) and High-risk cytogenetics (t(4;14), t(14;16), or del(17p)) or elevated LDH 10 40 LDH, lactate dehydrogenase. Derived from Palumbo A, et al. (2015). Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol, 33, 2863–9.

 ASCT is performed with melphalan 200 mg/m2 as the prepara- tive or conditioning regimen. This is followed by infusion of

the previously collected peripheral blood stem cells. In a randomized trial performed by the French Myeloma Group, ASCT was associ- ated with a higher rate of 5-year, event-free survival (28% vs 10%) and OS (52% vs 12%) compared with standard dose chemotherapy. Other trials have subsequently confirmed the value of ASCT in mye- loma. The timing of ASCT has been studied, and OS appears similar whether ASCT is performed as part of initial therapy or at first re- lapse. Thus in standard-risk myeloma, the choice of early versus delayed ASCT can be offered to patients if adequate resources are available for cryopreservation of stem cells. A randomized trial of 399 previously untreated myeloma pa- tients under 60 years of age from France found significantly im- proved 7-year event-free survival (20% vs 10%) and OS (42% vs 21%) in recipients of double versus single ASCT. However this trial was done prior to the arrival of new agents, and the benefit of double ASCT was mainly seen in patients who had not achieved very good partial response with the first transplant. Since most pa- tients achieve an excellent response even prior to the first ASCT with novel regimens such as VRD, the role of double ASCT in mye- loma has diminished greatly. Allogeneic bone marrow transplantation Unfortunately, allogeneic bone marrow transplantation has not consistently shown a benefit in myeloma, and it is associated with high mortality and morbidity rates. Hence the procedure is mainly investigational, and outside of a trial setting reserved for selected young patients with high-risk disease that has relapsed after initial therapy and ASCT. Maintenance therapy The role of consolidation and maintenance after ASCT has been studied extensively in myeloma. Most initial trials were Table 22.4.6.5 Major treatment regimens in plasma cell myeloma Regimen Usual dosing schedulea Doublets Lenalidomide–dexamethasone (Rd) Lenalidomide 25 mg orally days 1–21 every 28 days Dexamethasone 40 mg orally days 1, 8, 15, 22 every 28 days Repeated every 4 weeks Pomalidomide–dexamethasone (Pom/Dex) Pomalidomide 4 mg days 1–21 Dexamethasone 40 mg orally on days on days 1, 8, 15, 22 Repeated every 4 weeks Triplets Bortezomib–thalidomide– dexamethasone (VTD)b Bortezomib 1.3 mg/m2 intravenous days 1, 8, 15, 22 Thalidomide 100–200 mg orally days 1–21 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 4 weeks × 4 cycles as pretransplant induction therapy Bortezomib–cyclophosphamide– dexamethasoneb (VCD or CyBorD) Cyclophosphamide 300 mg/m2 orally on days 1, 8, 15, and 22 Bortezomib 1.3 mg/m2 intravenously on days 1, 8, 15, 22 Dexamethasone 40 mg orally on days on days 1, 8, 15, 22 Repeated every 4 weeksc Bortezomib–lenalidomide– dexamethasone (VRD)b Bortezomib 1.3 mg/m2 intravenously days 1, 8, 15 Lenalidomide 25 mg orally days 1–14 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 3 weeksd Carfilzomib– cyclophosphamide–dexamethasone (CCyD)e Carfilzomib 20 mg/m2 (cycle 1) and 36 mg/m2 (subsequent cycles) intravenously on days 1, 2, 8, 9, 15, 16 Cyclophosphamide 300 mg/m2 orally on days 1, 8, 15 Dexamethasone 40 mg orally on days on days 1, 8, 15 Repeated every 4 weeksc Carfilzomib–lenalidomide– dexamethasone (KRD) Carfilzomib 27 mg/m2 intravenously on days 1, 2, 8, 9, 15, 16 (note: cycle 1, day 1 and 2 carfilzomib dose is 20 mg/m2) Lenalidomide 25 mg orally days 1–21 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 4 weeks Carfilzomib–pomalidomide– dexamethasone Carfilzomib 27 mg/m2 intravenously on days 1, 2, 8, 9, 15, 16 (note: cycle 1, day 1 and 2 carfilzomib dose is 20 mg/m2) Pomalidomide 4 mg orally days 1–21 Dexamethasone 40 mg days 1, 8, 15, 22 Repeated every 4 weeks a All doses need to be adjusted for performance status, renal function, blood counts, and other toxicities. b Doses of dexamethasone and/or bortezomib reduced based on subsequent data showing lower toxicity and similar efficacy with reduced doses. c The day 22 dose of all three drugs is omitted if counts are low, or after initial response to improve tolerability, or when the regimen is used as maintenance therapy; when used as maintenance therapy for high-risk patients, further

delays can be instituted between cycles. d Omit day 15 dose if counts are low or when the regimen is used as maintenance therapy; when used as maintenance therapy for high-risk patients, lenalidomide dose may be decreased to 10–15 mg per day, and delays can be instituted between cycles as done in total therapy protocols. e Dosing based on trial in newly diagnosed patients; in relapsed patients cycle 2 carfilzomib dose is 27 mg/m2 consistent with approval summary. Modified from Rajkumar SV (2014). Multiple myeloma: 2014 update on diagnosis, risk-stratification, and management. Am J Hematol, 89, 998–1009. Copyright © 2014, John Wiley and Sons.

section 22 Haematological disorders 5318 disappointing. More recent studies with lenalidomide and with bortezomib have however shown promise. McCarthy et al., found superior PFS and OS with lenalidomide maintenance compared with placebo; the OS survival at 3 years was 88% with lenalidomide and 80% in the placebo regimen (hazard ratio 0.62). However, Attal and colleagues in a similar trial found that PFS was longer, 41 months with maintenance lenalidomide and 23 months for placebo, but OS was virtually the same. These data are conflicting, and the un- answered question is whether patients who start lenalidomide at the first sign of relapse may do as well (with fewer adverse effects) com- pared with patients who start it at the outset following ASCT. One concern about routine post-ASCT maintenance is that there was an excess risk of secondary cancers in both trials in patients receiving lenalidomide maintenance compared with placebo. At this point, we are hesitant to recommend lenalidomide maintenance to all pa- tients. Lenalidomide maintenance can be considered post ASCT, es- pecially in standard-risk myeloma patients who have not achieved a very good partial response following ASCT. In high-risk myeloma, bortezomib maintenance appears promising. In a randomized trial, patients receiving 2 years of bortezomib given every other week as post-transplant maintenance had superior outcomes compared with those receiving thalidomide maintenance. Following ASCT, and during the observation/maintenance phase, patients should be monitored closely every 3 to 4 months. The me- dian time at which relapse occurs is approximately 2 years in pa- tients not receiving maintenance, and 4 years in patients receiving maintenance. Patients not eligible for stem cell transplantation Initial therapy for patients who are considered to be not eligible for ASCT is usually given for approximately 12 months. We prefer VRD or daratumumab, lenalidomide, dexamethasone (DRD) in fit pa- tients, and Rd in patients who are frail. Following initial therapy, maintenance is usually administered. In patients who are treated with VRD, treatment is continued for 9–12 months and is then fol- lowed by lenalidomide maintenance (standard risk myeloma) or bortezomib maintenance (high risk myeloma). In patients treated with DRD, the same regimen is continued with a lower intensity after the first 6 months. Treatment of relapsed refractory myeloma Patients with myeloma undergo multiple remissions and relapses. Each remission is typically shorter than the previous one. As the number of new drugs increases, so does the number of available combinations to treat relapse. Some key principles are important to keep in mind when treating relapse. First, in general, treatment started at relapse is continued until progression. However, in some regimens such as those using carfilzomib or alkylators it may be reasonable to stop therapy with these drugs once a stable plateau has been reached in order to minimize risks of serious toxicity. Second, the choice of the regimen is based on the aggressiveness of the relapse. Thus patients with more aggressive relapse may require a multidrug regimen, more indolent relapses can some- times be managed with doublets or triplets. Third, in eligible pa- tients, ASCT should be included in the consideration if the patient has never had an ASCT, or if the remission duration with a prior ASCT exceeds 18 months (unmaintained) or 36 months (with maintenance). New agents approved for the treatment of relapsed myeloma include carfilzomib, pomalidomide,

panobinostat, daratumumab, elotuzumab, and ixazomib. The most common regimens and new drugs used in the treatment of relapsed refractory myeloma are discussed in the following sections. These drugs used alone and in combination are the principal options for the treatment of relapse. Regimens used in initial therapy In patients who relapse, the regimens listed as options for initial therapy such as VRD, DRD, VTD, VCD, etc. can all be considered. If patients had responded well to a given regimen, and then re- lapsed months to years after stopping therapy, the same regimen can be reinstituted. Alternatively, a regimen substantially different than the one used for initial therapy can be tried; for example, DRD in a patient who is relapsing after initial therapy with VRD. Triplet regimens such as VRD, DRD, and VCD are well tolerated when low-dose dexamethasone and weekly subcutaneous bortezomib schedules are used. Carfilzomib Carfilzomib is a keto-epoxide tetrapeptide proteasome inhibitor that has shown efficacy in relapsed myeloma. In a phase III trial of 792 patients, carfilzomib, lenalidomide, and dexamethasone (KRd) was associated with better response rates, PFS, and OS compared with Rd. PFS was 26.3 months with KRD versus 17.6 months in the control group (P = 0.0001). Support for carfilzomib as a more potent proteasome inhibitor than bortezomib comes from a randomized trial in which carfilzomib/dexamethasone demonstrated a doub- ling of PFS compared with bortezomib/dexamethasone in relapsed myeloma; PFS of 18.7 months versus 9.4 months, respectively (P <0.001). However, the dose of carfilzomib used in this trial (56 mg/ m2) is much higher, and carries a much higher monetary cost com- pared with bortezomib. Carfilzomib has lower neurotoxicity than bortezomib, but a small proportion (5%) of patients may experience serious cardiac side effects. Pomalidomide Pomalidomide is an analogue of lenalidomide and thalidomide with significant activity in relapsed refractory myeloma, even in patients failing lenalidomide and bortezomib. In a randomized trial of 302 patients with refractory myeloma, pomalidomide plus low-dose dexamethasone was found superior to high-dose dexamethasone. The doublet regimen of Pd is a reasonable option for patients with indolent relapse. Pomalidomide can also be administered in com- binations such as carfilzomib, pomalidomide, and dexamethasone (car/pom/dex). Panobinostat Panobinostat is a pan-deacetylase inhibitor that blocks the aggresome pathway, an alternative route for cells to bypass the le- thal effects of proteasome inhibition. By combining bortezomib and panobinostat, there is simultaneous blockade of both proteasome and aggresome pathways. In a randomized trial of 768 patients, bortezomib/dexamethasone plus panobinostat was associated with superior PFS compared with bortezomib/dexamethasone plus pla- cebo. However, panobinostat was associated with grade 3 diarrhoea in approximately 25% of patients, and care should be exercised when using this drug.

22.4.6 Plasma cell myeloma and related monoclonal gammopathies 5319 Elotuzumab Elotuzumab, a monoclonal antibody targeting the signalling lymphocytic activation molecule F7 (SLAMF7), does not have any single-agent activity, but synergizes with Rd. In a phase III trial of 646 patients, elotuzumab plus Rd was superior to Rd in terms of PFS, median PFS 19.4 months versus 14.9 months, respectively (P <0.001). Elotuzumab is well tolerated. Daratumumab Daratumumab, a monoclonal antibody targeting CD38, has shown promise in relapsed, refractory myeloma. In a phase II trial, daratumumab as a single agent produced a response rate of approxi- mately 30% in heavily pretreated patients. In randomized trials, DRD and daratumumab, bortezomib, dexamethasone (DVD) have shown superiority over doublet regimens. Ixazomib Ixazomib is an oral proteasome inhibitor that is active in relapsed myeloma. In a randomized controlled trial in relapsed myeloma, ixazomib, lenalidomide, and dexamethasone (IRd) was found to im- prove PFS compared with Rd. Ixazomib needs to be administered only once weekly, a major advantage when

considering long-term therapy. It has lower risk of neurotoxicity compared with bortezomib. Emerging options Promising agents in development for myeloma include marizomib, a new proteasome inhibitor, oprozmib, an oral proteasome inhibitor related to carfilzomib; filanesib, a kinesin spindle protein inhibitor; dinaciclib, a cyclin-dependent kinase inhibitor; venetoclax, a selective BCL-2 inhibitor, and LGH-447, a pan PIM kinase inhibitor. Each of these drugs has single-agent activity in relapsed myeloma. Supportive care Skeletal complications Bisphosphonates are important for the treatment of patients with plasma cell myeloma and associated bony disease. Pamidronate 90 mg intravenously over at least 2 h or zoledronic acid 4 mg over at least 15 min every 3 to 4 weeks are recommended. Intravenous bisphosphonates should be continued for 1 to 2 years and if the patient has stable disease, bisphosphonates may be discon- tinued. Bisphosphonates should be resumed upon relapse with new skeletal-related events. Other potential side effects of intra- venous bisphosphonates include the development of proteinuria or, rarely, acute kidney injury. Osteonecrosis of the jaw has also been described. Denosumab, is an alternative to bisphosphonates in pa- tients with renal dysfunction. Both vertebroplasty (injection of methyl methacrylate into a collapsed vertebral body) and kyphoplasty (introduction of an inflatable bone tamp into the vertebral body and after inflation, the injection of methyl methacrylate into the cavity) have been used to decrease pain and help restore vertebral height. Pain relief is gener- ally rapid and may be long-lasting. Patients should be encouraged to be as active as possible, but they must avoid undue trauma. Fixation of fractures or pending fractures with an intramedullary rod and methyl methacrylate has produced good results. Bone pain should be treated with analgesics or nar- cotics as necessary. Hypercalcaemia This is present in 15% of patients at diagnosis and should be sus- pected in the presence of anorexia, nausea, vomiting, polyuria, polydipsia, constipation, weakness, confusion, or stupor. If un- treated, renal insufficiency develops. Hydration with saline, cor- ticosteroids, and intravenous bisphosphonates are the mainstay of therapy. Calcitonin may be helpful if the patient is refractory to bisphosphonates. Haemodialysis may be useful in some patients with severe, resistant hypercalcaemia. The dose of zoledronic acid must be reduced in patients with renal failure. Light-chain cast nephropathy Maintenance of a high urine output (3 litres/day) is important. Nonsteroidal anti-inflammatory agents, dehydration, infections, or radiographic contrast media may contribute to acute kidney injury and should be avoided. Patients with acute or subacute kidney injury should be treated with a regimen such as VCD or VTD to reduce the tumour mass as quickly as possible. Plasmapheresis may be useful in acute kidney injury, but patients with irreversible changes are un- likely to benefit. Haemodialysis or peritoneal dialysis is necessary in the event of symptomatic azotaemia. Infection Appropriate antibiotic therapy for bacterial infections is essential. Patients should receive pneumococcal and influenza vaccination despite their suboptimal antibody response. Prophylaxis against pneumocystis pneumonia should be considered in patients re- ceiving high-dose corticosteroids. Intravenously administered gammaglobulin can be used for severe recurrent infections. Neurological Spinal cord compression should be suspected in patients with back pain who develop weakness or paraesthesiae of the lower extrem- ities or bladder or bowel dysfunction. Imaging by MRI or CT must be performed immediately. Radiation therapy and dexametha- sone are usually effective, and surgical decompression is rarely necessary. Hyperviscosity This is characterized by oral or nasal bleeding, blurred vision, paraes- thesiae, headache, reduced cerebration, or congestive heart failure. Serum viscosity levels do not correlate well with the symptoms or clinical findings. Plasmapheresis promptly relieves the symptoms and should be done regardless of the viscosity level if the patient has signs or symptoms of hyperviscosity. Anaemia Anaemia occurs in almost all patients during the course of myeloma. Erythropoietin (40 000 U

subcutaneously weekly) or darbepoetin (200 µg subcutaneously every 2 weeks) is beneficial. Blood transfusions are indicated for patients with symptomatic anaemia who do not benefit from other therapy. Iron, folate, or vitamin B12 deficiency may be responsible for anaemia and must be recognized and treated. Emotional support All patients with myeloma need substantial and continuing emo- tional support. The physician's approach must be positive and

 emphasize the potential benefits of therapy. It is reassuring for pa- tients to know that many survive for 10 years or more. It is vital that the physician caring for patients with myeloma has the interest and capacity to deal with an incurable disease over the space of years with assurance, sympathy, and resourcefulness. Variant forms of plasma cell myeloma Plasma cell leukaemia Plasma cell leukaemia is defined as the presence of more than 5% plasma cells in the peripheral blood on regular white blood cell dif- ferential count examination. It is classified as primary when it pre- sents de novo (60% of cases) and as secondary when it is a leukaemia transformation of previously recognized plasma cell myeloma (40%). Patients with primary plasma cell leukaemia are younger and have a higher platelet count, fewer bone lesions, a smaller serum paraprotein, a greater incidence of hepatosplenomegaly and lymph- adenopathy, and a longer duration of survival than patients with sec- ondary plasma cell leukaemia. Cytogenetic abnormalities are more common than in patients with plasma cell myeloma. Treatment is with multidrug initial therapy followed by ASCT and bortezomib- based maintenance. Those with secondary plasma cell leukaemia rarely respond to chemotherapy because they already have received treatment and are refractory. POEMS syndrome (osteosclerotic myeloma) This is characterized by polyneuropathy (P), organomegaly (O), endocrinopathy (E), M-protein (M), and skin changes (S) (Table 22.4.6.1). The major clinical finding is a chronic inflammatory– demyelinating neuropathy with predominantly motor disability. Sclerotic bone lesions are found in almost all patients. The cranial nerves are not involved except for the presence of papilloedema, which is seen in 30 to 40%. Hepatomegaly occurs in almost half of patients, but splenomegaly and lymphadenopathy occur in a mi- nority. Hyperpigmentation and hypertrichosis are frequent but may be easily overlooked. Gynaecomastia and atrophic testes as well as clubbing of the fingers and toes may be present. Angiomatous le- sions of the trunk are often prominent. Pulmonary hypertension has been recognized in several instances. Ascites, pleural effusion, and peripheral oedema may be present. In contrast to plasma cell myeloma, the haemoglobin level is usually normal or increased, and thrombocytosis is common. The bone marrow usually contains fewer than 5% monoclonal plasma cells, and hypercalcaemia and renal insufficiency rarely occur. Almost all patients have a λ light chain, and IgA is the most common heavy-chain type. Castleman's disease may be present. Vascular endothelial growth factor levels may be 5- to 10-fold higher in POEMS syndrome compared with normal controls. If the skeletal lesions are in a limited area, radiation almost always produces a substantial improvement of the neur- opathy. If widespread osteosclerotic lesions exist, an ASCT should be considered for therapy. Chemotherapy similar to that used in mye- loma may be helpful. The median survival is approximately 15 years. Solitary plasmacytoma of bone The diagnosis depends on histological evidence of a plasma cell tumour but no evidence of multiple myeloma (Table 22.4.6.1). A small M-protein may be found in the serum or urine, but it usually disappears after radiation of a solitary lesion. In a study of 116 patients with solitary plasmacytoma of bone, the persist- ence of a serum M-protein level of 5 g/litre or more 1 to 2 years after diagnosis and an abnormal FLC ratio at the time of diagnosis are predictive of disease progression. Some patients may have up to 10% clonal plasma cells, and are considered to have both soli- tary plasmacytoma with minimal marrow involvement. Treatment

consists of tumouricidal radiation (40–50 Gy). Progression to overt myeloma develops in approximately 10% of patients with solitary plasmacytoma, and in 60% of patients with solitary plasmacytoma with minimal marrow involvement over the next 3 years. Baseline PET-CT and/or MRI scans are helping in making the accurate diagnosis at the outset. Solitary extramedullary plasmacytoma This is a plasma cell tumour that arises outside the bone marrow. It is located in the upper respiratory tract in approximately 80% of cases, and the nasal cavity and sinuses, nasopharynx, and larynx are most often involved. The gastrointestinal tract, central nervous system, urinary bladder, thyroid, breast, testes, parotid gland, and lymph nodes have all been reported as the initial site of an extramedullary plasmacytoma. There is a predominance of IgA M-protein in extramedullary plasmacytomas. The diagnosis de- pends on the finding of a plasma cell tumour in an extramedullary location and the absence of myeloma on bone marrow examin- ation, radiography, and appropriate studies of serum and urine. Treatment consists of tumouricidal radiation (40–50 Gy). Regional occurrences develop in approximately 10% of patients, while development of typical plasma cell myeloma occurs in 20%. Waldenström's macroglobulinaemia This malignant lymphoplasmacytic proliferative disorder produces a high concentration of immunoglobulin M (IgM) paraprotein. It bears similarities to myeloma, lymphoma, and chronic lympho- cytic leukaemia. The incidence rate is 0.5/100 000. The median age is approximately 65 years, and 60% of patients are male. Clinical findings Weakness and fatigue are the most common symptoms of WM. Chronic nasal bleeding or oozing from the gums is character- istic, but postsurgical or gastrointestinal bleeding may also occur. Blurring or loss of vision may be prominent. Dyspnoea and con- gestive heart failure may develop. Dizziness, headaches, vertigo, nystagmus, ataxia, and diplopia have been seen. Constitutional symptoms including fever, night sweats, and loss of weight may be present. Bone pain is rare. Hepatomegaly occurs in about 25% of patients at diagnosis, and splenomegaly and lymphadenopathy are slightly less common. Retinal vein engorgement and flame- shaped haemorrhages are common and are a better measure of symptomatic hyperviscosity syndrome than is the measurement of serum viscosity. Pulmonary involvement may be manifested by diffuse pulmonary infiltrates, isolated masses, or pleural effusion. Retroperitoneal and mesenteric lymphadenopathy are common, but they are usually asymptomatic. The most common neurological manifestation is sensorimotor peripheral neuropathy. It is related to amyloid depos- ition in some instances.

22.4.6 Plasma cell myeloma and related monoclonal gammopathies 5321 Laboratory findings Anaemia is found in most patients with symptomatic WM. Spuriously low haemoglobin and haematocrit levels may re- sult from an increased plasma volume due to the large amount of paraprotein. Serum protein electrophoresis reveals a tall, narrow spike or dense band usually migrating in the γ area. About 75% of the IgM paraproteins are κ. The IgM level obtained by nephelometry is often 10 to 30 g/litre more than that found with serum protein electrophor- esis. A reduction of uninvolved IgG and IgA immunoglobulins is less striking than in multiple myeloma. About 10% of macroglobulins precipitate in the cold (cryoglobulin) but are almost always asymptomatic. A monoclonal light chain detected by immunofixation is present in the urine in 75% of patients, but it is usually small. The bone marrow aspirate is often hypocellular, but the biopsy specimen is usually hypercellular and extensively infiltrated with lymphoid or plasmacytoid cells (lymphoplasmacytic lymphoma). Increased mast cells are frequently present. Diagnosis WM arises from CD25+CD22+low activated B lymphocytes. The diagnosis of WM depends on the presence of an IgM paraprotein and a 10% or greater monoclonal lymphoplasmacytic infiltration of the bone marrow producing symptoms and physical findings consistent with WM. The lymphoplasmacytic

cells express CD19, CD20, and CD22. Most patients with WM have a recurrent somatic mutation, L265P, involving the MYD88 gene. The differential diag- nosis includes plasma cell myeloma, MGUS of the IgM type, smoul- dering WM, chronic lymphocytic leukaemia, lymphoma, and other undifferentiated lymphoplasmacytic proliferative disorders. A var- iety of prognostic models have been reported. Treatment Patients with WM should not be treated unless they are symptom- atic. Even in the presence of 10% or more clonal infiltration of the bone marrow, patients without end-organ damage can remain stable without therapy for extended periods of time. Such patients, some- times termed smouldering WM, occupy a clinical stage in between IgM MGUS and WM. In symptomatic patients, therapy involved rituximab-based combinations. Rituximab, a monoclonal antibody directed against the CD20 antigenic determinant, produces a response in approxi- mately one-half of patients. It is often given with dexamethasone and cyclophosphamide, or with bendamustine. The IgM levels may temporarily increase following therapy (flare). The response to rituximab may be delayed and maximum response may not occur until several months after therapy. Symptoms and findings of hyperviscosity are quickly controlled by plasmapheresis with a cell separator. Options for therapy of relapsed WM besides regimens used in the frontline setting include ibrutinib, bortezomib plus rituximab and dexamethasone, purine nucleoside analogues (cladribine, fludarabine), carfilzomib, and immunomodulatory agents (thal- idomide, lenalidomide). Ibrutinib is an irreversible and selective inhibitor of Bruton tyrosine kinase, a signalling molecule in the B-cell antigen receptor cascade. In a phase II study including 63 patients with symptomatic relapsed/refractory WM, the overall response rate was 81%. Chlorambucil, given continuously or intermittently, has been a standard treatment for more than 50 years, but has now fallen out of favour. Everolimus (RAD-001), perifosine, or alemtuzumab, an anti-CD52 antibody, have all shown activity. The median duration of survival for patients with WM is more than 5 years. Heavy-chain diseases Heavy-chain diseases are clonal plasma cell disorders where intact IgH is secreted without any companion light chain. These disorders are rare, and very few data are available on optimal therapy. γ-Heavy-chain diseases The paraprotein consists of a monoclonal γ chain with significant amino acid deletions. The initial presentation is often a lymphoma- like illness, but the symptoms and clinical findings are diverse and range from an aggressive lymphoproliferative process to an asymp- tomatic state. Weakness, fatigue, and fever are the most common presenting symptoms. The serum protein electrophoretic pattern usually shows a broad-based band more suggestive of a polyclonal than an M-protein. Symptomatic patients should be treated with chemotherapy regimens similar to ones used on non-Hodgkin’s lymphoma. The median duration of survival in a series of 23 patients was 7.4 years (range 1 month to 21 years). α-Heavy-chain diseases α-Heavy-chain disease is the most common type of heavy-chain disease, with more than 400 reported patients since its recogni- tion. Most patients have been from relatively poor countries in the Mediterranean region and Middle East. Gastrointestinal tract involvement is most common and is manifested by malabsorp- tion with loss of weight, diarrhoea, and steatorrhoea. It is similar to ‘immunoproliferative small intestinal disease’ (IPSID). The serum protein electrophoretic pattern shows no spike. The diag- nosis depends on recognition of a monoclonal α heavy chain in the serum or jejunal fluid. α-Heavy-chain disease is progressive and fatal without therapy. Antibiotics may produce remission, particularly if given early in the course of the disease. Patients who have advanced disease or who do not respond to antibiotics should be treated with a combination of chemotherapy consisting of chemotherapy regimens similar to ones used on non-Hodgkin lymphoma. μ-Heavy-chain diseases μ-Heavy-chain disease is characterized by the presence of a mono- clonal μ-chain fragment in the serum. Most patients have a chronic lymphoproliferative process resembling chronic lymphocytic leu- kaemia or lymphoma. Fewer than

40 cases have been reported. The serum protein electrophoretic pattern contains a spike or localized band in about 40% of patients. Vacuolization of the plasma cells in the marrow is an important clue for the diagnosis of μ-heavy-chain disease. The course of μ-heavy-chain disease is variable, with a me- dian survival of approximately 2 years. Patients should be treated with chemotherapy regimens similar to ones used on non-Hodgkin lymphoma.

section 22 Haematological disorders 5322 Immunoglobulin light-chain amyloidosis Amyloid is a substance consisting of fibrils that appear homoge- neous and amorphous under the light microscope and stain pink with haematoxylin–eosin. With polarized light, amyloid stained with Congo red produces an apple-green birefringence. Linear, nonbranching, aggregated fibrils 7.5 to 10 nm wide and of indef- inite length are seen with electron microscopy. In AL amyloidosis, these fibrils consist of monoclonal κ or λ light chains. Other forms of amyloidosis exist, and are caused by a variety of different pro- teins such as protein A in secondary amyloidosis, transthyretin (prealbumin) in familial or senile systemic amyloidosis, and β2- microglobulin in dialysis-associated amyloidosis. More than 25 dif- ferent proteins may form amyloid fibrils. Only AL amyloidosis is a monoclonal gammopathy; the other forms are not related to plasma cell disorders and are not discussed here. Aetiology and epidemiology The annual incidence of AL amyloidosis is 0.9/100 000. The median age at diagnosis is 65 years, and only 1% of patients are younger than 40 years. The cause of AL amyloidosis is unknown. Clinical features The clinical features depend on the specific organ involved, and the number of organs that are involved in AL. Weakness, fatigue, and weight loss are the most common initial symptoms. Light- headedness, syncope, change in the tongue or voice, jaw or hip claudication, paraesthesiae, dyspnoea, and oedema are the most frequent symptoms. Macroglossia is present in 10% of patients, and purpura, particularly in the periorbital and facial areas, is found in 15%. The liver is palpable in 25% of patients, but spleno- megaly occurs in only 5%. Nephrotic syndrome or renal failure is found in more than 25% of patients at diagnosis (Fig. 22.4.6.5). Congestive heart failure, carpal tunnel syndrome, sensorimotor peripheral neuropathy, and orthostatic hypotension are other important features. The presence of one of these syndromes and concomitant presence of an M-protein are strong indications of AL, for which appropriate biopsy specimens must be taken for diagnosis. Laboratory findings The serum protein electrophoretic pattern shows a modest-sized lo- calized band or spike in about half of the patients (median 14 g/litre). An M-protein is found in the serum or urine in 90% of patients, and λ light chains are twice as common as κ. The bone marrow con- tains 5% or less monoclonal plasma cells in almost half of patients. A paraprotein in the serum or urine or a monoclonal proliferation of plasma cells in the bone marrow occurs in 98% of patients with AL amyloidosis. Only one-fifth of patients have more than 20% plasma cells in the bone marrow, but they usually do not have the other fea- tures of plasma cell myeloma. An increased serum alkaline phosphatase level is not un- common. Hyperbilirubinaemia is infrequent, but when present it is an ominous sign. The coagulation factor X concentration is decreased in more than 10% of patients but is rarely the cause of bleeding. Congestive heart failure is present in about 20% of patients at diagnosis. Electrocardiography frequently reveals low voltage in the limb leads or characteristics consistent with anteroseptal infarction (loss of anterior forces). Arrhythmias, including atrial fibrillation or heart block, are common. Almost two-thirds of patients have an abnormal echocardiogram at diagnosis. Early cardiac involvement is characterized by abnormal relaxation followed by the features of constrictive cardiomyopathy. Amyloid heart disease may closely resemble constrictive pericarditis or hypertrophic obstructive car- diomyopathy. A sensorimotor peripheral neuropathy is present in about 15% of patients at diagnosis. Autonomic dysfunction may be a prominent feature

and is often manifested by orthostatic hypoten- sion, diarrhoea, and impotence. Diagnosis The diagnosis depends on appropriate systemic syndrome, evi- dence of a monoclonal plasma cell disorder, the demonstration of amyloid deposits, and mass spectroscopy showing that the fibrils are composed of immunoglobulin light chains. The pos- sibility of AL amyloidosis must be considered in patients who have an M-protein in the serum or urine and who present with unexplained nephrotic syndrome, congestive heart failure, sen- sorimotor peripheral neuropathy, carpal tunnel syndrome, hep- atomegaly, or malabsorption syndrome. The initial diagnostic procedure should be an abdominal fat aspiration, which is posi- tive in about 75% of patients (Fig. 22.4.6.6). A bone marrow as- piration and biopsy should be done to determine the degree of plasmacytosis, and amyloid stains of the biopsy specimen will be positive in slightly more than half of patients. The abdominal fat aspirate and/or bone marrow biopsy is positive in 90% of cases; if negative, a biopsy of a suspected involved organ such as the kidney, liver, heart, or sural nerve is indicated. We perform laser microdissection of Congo Red staining material from the biopsy specimens embedded in paraffin and then subject the specimen to tandem mass spectrometry-based proteomic analysis. Iodine-123 labelled serum amyloid-P component scintigraphy can be used for identifying and monitoring the extent of systemic amyloidosis but it is not readily available. 40 20 0 Positive (%) 10 30 2 5 0.5 0.5 17 21 17 28 Nephrotic/ renal failure n = 142 CHF n = 104 Carpal tunnel n = 102 Peripheral neuropathy n = 81 Ortho hypo n = 58 11 1.5 At diagnosis During follow-up n = 474 Fig. 22.4.6.5 Frequency of amyloid syndromes at diagnosis of immunoglobulin light chain amyloidosis. CHF, congestive heart failure; Ortho hypo, orthostatic hypotension. From Kyle RA, Gertz MA (1995). Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol, 32, 45–59. By permission of
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 Prognosis The median duration of survival for 474 patients with AL within 1 month of diagnosis was 13 months. Those presenting with con- gestive heart failure had a median survival of 4 months. Elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), as well as cardiac troponins are important prognostic features. In 261 patients with newly diagnosed AL amyloidosis, the sur- vival was 6 months in patients with a detectable level of cardiac troponin T compared with 22 months for those who did not. A prognostic model consisting of NT-proBNP greater than 332 mg/litre and cardiac troponin T greater than 0.035 mcg/litre were classified as stages I, II, or III, depending on whether none, one, or both NT-proBNP and cardiac troponins were above these levels. The survivals for stages I, II, and III were 26, 11, and 4 months, respectively. Treatment The goal of therapy in AL amyloidosis is to eradicate the plasma cell clone responsible for the monoclonal light chain production. This is achieved with therapy similar to that used in plasma cell myeloma. Specifically VCD is used as initial therapy in most patients. In eli- gible patients without cardiac or multiorgan involvement, ASCT is an option. But even with careful selection, the 100-day treatment related mortality is approximately 5%, in contrast to 1 to 2% for mul- tiple myeloma. There are emerging data that doxycycline may pro- long survival in AL amyloidosis by inhibiting deposition of amyloid fibrils. Trials are also ongoing with other agents in an attempt to pre- vent amyloid fibril deposition. Future directions Despite the introduction of several new agents, plasma cell myeloma and related disorders remain incurable in most patients. A better understanding of disease biology and identification of new drugs in the last 10 years has dramatically improved OS. Additional prom- ising treatment options are certain to emerge. At present, there are also trials going on to determine if early therapy at the SM stage can lead to a cure. Some of the problem areas requiring

additional attention include treatment of high-risk myeloma, plasma cell leu- kaemia, extramedullary relapse, and AL amyloidosis. Prediction of response to therapy may lead to more personalized care and is a major goal for the future. FURTHER READING Attal M, et al. (1996). A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple mye- loma. Intergroupe Francais du Myelome. N Engl J Med, 335, 91–7. Attal M, et al. (2012). Lenalidomide maintenance after stem-cell trans- plantation for multiple myeloma. N Engl J Med, 366, 1782–91. Benboubker L, et al. (2014). Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med, 371, 906–17. Dispenzieri A, et al. (2013). Prevalence and risk of progression of light- chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. Lancet, 375, 1721–8. Falk RH, Comenzo RL, Skinner M (1997). The systemic amyloidoses. N Engl J Med, 337, 898–909. Krishnan A, et al. (2011). Autologous haemopoietic stem-cell trans- plantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. Lancet Oncol, 12, 1195–203. Kumar S, et al. (2012). Trisomies in multiple myeloma: impact on sur- vival in patients with high-risk cytogenetics. Blood, 119, 2100–5. Kumar SK, et al. (2014). Continued improvement in survival in mul- tiple myeloma: changes in early mortality and outcomes in older pa- tients. Leukemia, 28, 1122–8. Kyle RA (2000). Multiple myeloma: an odyssey of discovery. Br J Haematol, 111, 1035–44. Kyle RA, Gertz MA (1995). Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol, 32, 45–59. Kyle RA, Rajkumar SV (2004). Multiple myeloma: drug therapy (re- view article). N Engl J Med, 351, 1860–73. Kyle RA, Rajkumar SV (2006). Monoclonal gammopathy of undeter- mined significance. Br J Haematol, 134, 573–89. Abdominal fat n = 212 100 80 60 40 20 0 Positive (%) 80 56 75 94 82 97 83 90 86 100 Bone marrow 394 Rectum 194 Kidney 81 Carpal ligament 20 Liver 32 Small intestine 23 Skin 19 Sural nerve 21 Heart 16 Fig. 22.4.6.6 Diagnosis of amyloidosis on the basis of deposits in tissues. From Kyle RA, Gertz MA (1995). Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol, 32, 45–59. By permission of W B Saunders Company.

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