

## CHAPTER 29

# Multiple myeloma

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### Definition

Multiple myeloma (MM) is characterized by the proliferation of a single clone of plasma cells that produce a monoclonal protein. The plasma cell proliferation results in extensive skeletal involvement, with osteolytic lesions, hypercalcaemia, anaemia and/or soft tissue plasmacytomas. In addition, the excessive production of nephrotoxic monoclonal immunoglobulin can result in renal failure and an increased risk of developing potentially life-threatening infections due to the lack of functional immunoglobulins. The clinical and laboratory manifestations of the disease, including their management, are discussed in this chapter.

### Epidemiology and aetiology

The annual incidence of MM is 4 per 100,000. It represents approximately 1% of all malignant diseases and 15% of all haematological malignancies. The incidence of MM is lower in Asian populations and in blacks is twice that in whites; MM is slightly more frequent in men than in women. The median age at diagnosis is 65–70 years. Only 15% and 2% of the patients are younger than 50 and 40 years, respectively.

The cause of MM is unknown. Radiation may play a role in some cases. An increased risk has been reported in farmers, particularly those who use herbicides and insecticides, and in people exposed to benzene and other organic solvents. However, the number of cases is small and more data are needed to establish a significant relationship. MM and monoclonal gammopa-

thy of undetermined significance (MGUS) have been reported in familial clusters. A relationship between MM and pre-existing inflammatory diseases has been suggested, and plasma cell dyscrasias associated with protracted stimulation of the reticuloendothelial system have been reported in experimental studies. However, more recent case-control studies do not support a role for chronic antigenic stimulation in the aetiopathogenesis of MM. There is now clear evidence that most, if not all, myeloma cases are preceded by a previous MGUS.

### Pathogenesis

MM is a B-cell malignancy characterized by the accumulation of terminally differentiated clonal plasma cells in the bone marrow, the production of a monoclonal immunoglobulin detectable in serum and/or urine and the presence of lytic bone lesions. In order to understand the pathogenesis of MM, it is important to review not only the molecular changes involved in the development of the malignant clone, but also the mechanisms responsible for the interaction between the malignant plasma cells and their microenvironment, since they play a relevant role in bone destruction, tumour cell growth, survival, migration and drug resistance.

### Cellular origin of myeloma cells

Normal differentiation from early B cells to plasma cells is characterized by three B-cell-specific DNA remodelling mechanisms that modify immunoglobulin genes: VDJ rearrangement,

somatic mutation and class switch recombination. Rearrangements of the immunoglobulin genes of B-cell precursors to form a B-cell receptor (BCR) occur in the bone marrow, while antigen recognition, selection, somatic hypermutation and class switch recombination take place in the germinal centre lymph node. Sequence analysis of the immunoglobulin VH gene support the postgerminal origin of myeloma cells, which have successfully completed somatic hypermutation (without intraclonal variation) and IgH switching, before migrating to the bone marrow, where they will interact with stromal cells before finally differentiating into long-lived plasma cells.

## Genomic abnormalities

Genome instability is a prominent feature of myeloma cells and in fact, almost all cases of MM are cytogenetically abnormal. Genomic abnormalities can be categorized as chromosomal translocations, mainly involving the *IGH* locus on chromosome 14q32, copy number abnormalities, mutations, methylation modifications, and gene and microRNA (miRNA) dysregulation.

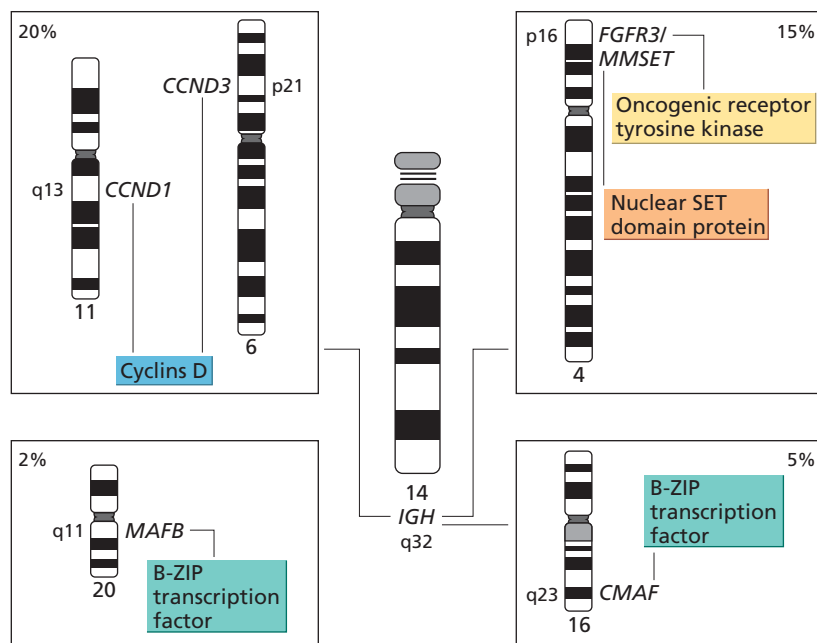
### *IGH* translocations

A primary event in many kinds of B-cell tumour is dysregulation of an oncogene that, as a result of translocation to the *IGH* locus (14q32) or, somewhat less often, the *IGL* locus ( $\kappa$  2p11 or  $\lambda$  22q11), is juxtaposed near one of the potent immunoglobulin enhancers. In MM, *IGH* translocation may be classified into primary or secondary. Primary *IGH* translocations occur as initiating events during the pathogenesis of MM, whereas secondary translocations are involved in progression. Most primary *IGH*

translocations result from errors in B-cell-specific DNA modification processes, mostly *IGH* switch recombination or, less often, somatic hypermutation. The breakpoints occur mainly within or immediately adjacent to *IGH* switch regions or JH regions. In contrast, secondary translocations are mediated by other kinds of recombination mechanism that do not specifically target B-cell-specific DNA modification processes. Unlike other B-cell tumours, in MM there is a marked diversity of chromosomal loci involved in *IGH* translocations. About 40% of MM tumours have *IGH* translocations involving five recurrent chromosomal patterns (Figure 29.1): 11q13 (*CCND1*), 4p16 (*FGFR/MMSET*), 16q23 (*MAF*), 6p21 (*CCND3*) and 20q11 (*MAFB*).

The prevalence of t(11;14) according to interphase fluorescence *in situ* hybridization (FISH) analysis is 15–20% and is readily detectable by karyotyping. As a result of the translocation, *CCND1* is juxtaposed to the powerful *IGH* 3' enhancer(s) on der(14), and its expression is dysregulated, as indicated by gene expression profiling and reverse transcriptase polymerase chain reaction (RT-PCR) in 100% of MM cases with t(11;14).

The t(4;14) translocation is identified in approximately 15% of MM cases using FISH analysis, but cannot be detected by karyotyping techniques. This translocation results in the simultaneous deregulation of the fibroblast growth factor receptor 3 (*FGFR3*) gene on der(14) and the multiple myeloma SET domain (*MMSET*) gene on der(4). *FGFR3* is one of the high-affinity tyrosine kinase receptors for the FGF family of ligands. Both *FGFR3* and *MMSET* genes are not normally expressed in plasma cells, but are over-expressed as a result of t(4;14). However, gene expression profiling and RT-PCR analysis have shown that only 75% of MM cases with t(4;14) display



**Figure 29.1** *IGH* translocations in multiple myeloma.

simultaneous over-expression of *MMSET* and *FGFR3*. In the remaining 25% of cases, only *MMSET* is upregulated and the lack of *FGFR3* expression is linked in most cases to loss of the *FGFR3* gene on der(14). These data suggest that *MMSET* may be the critical transforming event in MM harbouring t(4;14), whereas *FGFR3* could be dispensable. In some cases (10%) the translocated *FGFR3* contains activating mutations that may be involved in MM progression.

The incidence of t(14;16) is 5–10%. The breakpoints on 16q23 occur over a region 550–1350 kb centromeric to *MAF*. Taking into account such a long distance, it is still an open question whether or not *IGH* may act as enhancer for *MAF* in this translocation. Moreover, over-expression of *MAF* is observed in half of myeloma cases, while the prevalence of t(14;16) is low. The t(6;14) translocation has been found in a low proportion (3%) of MM cases. Using microarray analyses, high levels of cyclin D3 mRNA have been shown in cases with t(6;14) detected by FISH. The t(14;20) translocation leads to deregulation of *MAFB* (20q23), which, like *MAF*, encodes a B-ZIP transcription factor, but in contrast to t(14;16), *MAFB* translocations have structural features that indicate they are secondary translocations.

### Gains and losses of chromosomal material

Almost all MM cases are aneuploid, as evidenced by the measurement of DNA content by flow cytometry and cytogenetic techniques. Patients with MM may be grouped into two major categories, according to ploidy status assessed by karyotyping: the hyperdiploid group (more than 46/47 chromosomes) and the non-hyperdiploid group, composed of hypodiploid (up to 44/45 chromosomes), pseudodiploid (44/45 to 46/47) and near tetraploid (more than 74) cases. Non-hyperdiploid MM is characterized by a very high prevalence of *IGH* translocations involving the five recurrent partners. Likewise, monosomy/deletion 13 and gains on 1q occur predominantly in non-hyperdiploid MM. In contrast, the hyperdiploid group is associated with recurrent trisomies involving odd chromosomes (3, 5, 7, 9, 11, 15 and 19) and with a low incidence of structural chromosomal abnormalities. Similar associations have been observed on analysing DNA content by flow cytometry.

The loss of chromosome 13 is the most common monosomy in MM (40–50% of newly diagnosed patients). This abnormality shows a strong association with t(4;14) and t(14;16), deletion of 17p and gains on 1q. Chromosome 17p deletion, which includes loss of *TP53*, occurs at a lower frequency in newly diagnosed MM (5–10%), although the proportion is higher in advanced stages of the disease. Furthermore, 17p deletion is associated with extramedullary MM. Conventional cytogenetics, FISH and comparative genomic hybridization analysis have all demonstrated that lesions of chromosome 1 are the most common abnormalities in MM; mostly they are 1q gains, as the result of tandem duplications and jumping segmental duplications of the

chromosome 1q band. Recently, a large FISH study has demonstrated that 1p losses (especially 1p22 and 1p32 deletions) are also frequent in MM patients.

### Mutations detected by whole-genome sequencing

Whole-genome sequencing strategies have shown that there are approximately 35 non-synonymous mutations per myeloma sample. However, few recurrently mutated genes have been detected, apart from the well-known mutations in the ERK pathway. This is in agreement with other haematological malignancies, such as acute myeloid leukaemia, but is in contrast to hairy cell leukaemia and Waldenström's macroglobulinaemia, in which single unifying mutations are seen, *BRAF* and *MYD88*, respectively.

### Epigenetic modifications

Little is known about the epigenetic changes involved in MM pathogenesis. The most relevant epigenetic change revealed so far is the global DNA hypomethylation and gene-specific DNA hypermethylation in MM as compared to MGUS. Interestingly, patients with the t(4;14) translocation have increased gene-specific DNA hypermethylation compared with myeloma samples of other cytogenetic subgroups.

### Late genetic events

Some genetic changes in MM, such as secondary translocations, mutations, deletions and epigenetic abnormalities, are considered late oncogenic events and are associated with disease progression. Dysregulation of *MYC* is a paradigm for secondary translocations in MM. Most karyotypic abnormalities involving *MYC* correspond to complex translocations and insertions that often are non-reciprocal and frequently involve three different chromosomes. Activating *RAS* mutations are considered molecular markers of disease progression. Thus, the prevalence of activating *KRAS* and *NRAS* mutations is over 75% in MM cases at relapse. *TP53* inactivation, via either deletion or mutation, seems to be more frequently associated with disease progression. Methylation is an epigenetic change that has been described in MM and acts as an inactivating mechanism of the tumour-suppressor genes *CDKN2B* and *CDKN2A*. Although it has also been detected in MGUS, its prevalence is much higher in advanced MM and extramedullary forms of the disease.

### Molecular classification of MM based on gene expression profiling

Gene expression analysis of MM has confirmed the huge genetic diversity of this tumour. Recently, the classification of MM into seven different groups has been proposed. Each group displays a specific genetic signature and some of them are associated with a particular *IGH* translocation or ploidy status and with a characteristic clinical behaviour. Table 29.1 summarizes this

**Table 29.1** Molecular classification of multiple myeloma.

Group	Specific translocation	Frequency (%)	Cyclin D expression	Genetic signature	Prognosis	Other characteristics
1 PR	–	12	CCND2	↑ <i>CCNB1</i> , ↑ <i>CCNB2</i> , ↑ <i>MCM2</i> , ↑ <i>BUB1</i> , ↑ <i>MAGEA6</i> , ↑ <i>MAGEA3</i> , ↑ <i>GAGE1</i>	Unfavourable	Normal karyotypes
2 LB	–	11	CCND2	↑ <i>EDN1</i> , ↑ <i>IL6R</i> , ↓ <i>DKK1</i> , ↓ <i>FRZB</i>	Favourable	Lower number of bone lesions
3 MS	t(4;14) <i>FGFR3/MMSET</i>	18	CCND2	↑ <i>FGFR3</i> , ↑ <i>MMSET</i> , ↑ <i>PBX1</i> , ↑ <i>PAX5</i>	Unfavourable	
4 HY	–	26	CCND1	↑ <i>TRAIL</i> , ↑ <i>DKK1</i> , ↑ <i>FRZB</i> , ↓ <i>CKS1B</i>	Favourable	Hyperdiploid karyotype, bone lesions
5 CD-1	t(11;14) <i>CCND1</i> or t(6;14) <i>CCND3</i>	8	CCND1 or CCND3	↑ <i>CEBPB</i> , ↑ <i>NID2</i> , ↑ <i>SET7</i>	Favourable	
6 CD-2	t(11;14) <i>CCND1</i> or t(6;14) <i>CCND3</i>	17	CCND1 or CCND3	↑ <i>MS4A1</i> ( <i>CD20</i> ), ↑ <i>PAX5</i> , ↑ <i>CD27</i> , ↑ <i>CXCR4</i>	Favourable	
7 MF	t(14;16) <i>MAF</i> or t(14;20) <i>MAFB</i>	8	CCND2	↑ <i>MAF</i> , ↑ <i>MAFB</i> , ↑ <i>CXCR1</i> , ↑ <i>ITGB7</i> , ↓ <i>DKK1</i>	Unfavourable	Lower number of bone lesions

PR, proliferation; LB, low bone disease; MS, *MMSET*; HY, hyperdiploid; CD-1, *CCND1/CCND3*; CD-2, *CCND1/CCND3*; MF, *MAF/MAFB*.

classification, which connects genetic abnormalities, cell transcriptome and clinical features of patients.

### Dysregulation of cyclin D genes as a potential unifying event in MM pathogenesis

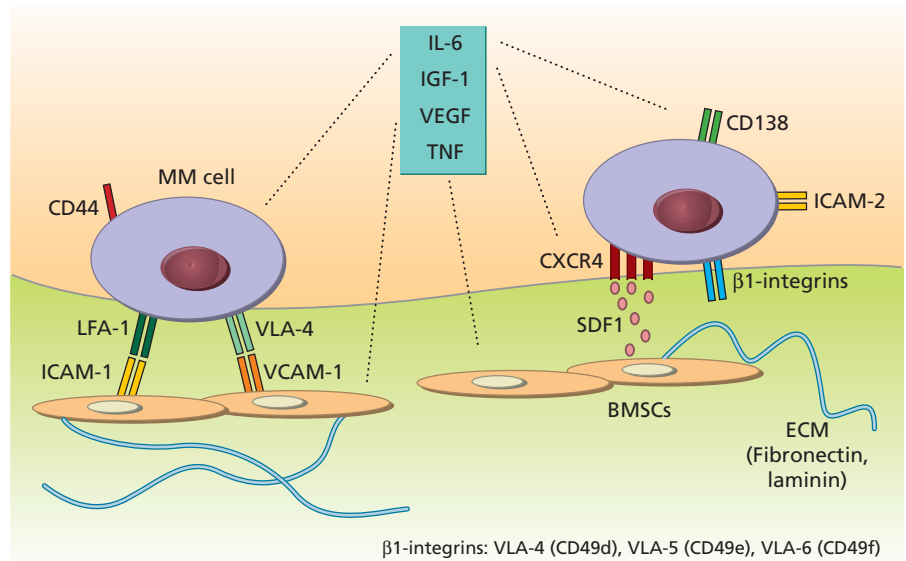
There is no common genetic mechanism to explain the pathogenesis of MM. However, it can be speculated that although *IGH* translocations induce upregulation of different oncogenes, it is possible that all *IGH* translocations involved in MM converge on a common pathway resulting in inhibition of differentiation and an increase in cell survival and proliferation. Gene expression profiling analysis has demonstrated that expression of *CCND1*, *CCND2* and *CCND3* is increased in virtually all MM patients, supporting the recent hypothesis of a potential unifying event in pathogenesis. Approximately 25% of MM cases display over-expression of one of these cyclins, which may be triggered directly by an *IGH* translocation such as t(11;14) and t(6;14) that dysregulates *CCND1* and *CCND3* respectively, or indirectly by an *IGH* translocation involving *MAF* and *MAFB* genes, which encode a transcription factor that targets cyclin D2. Nearly 40% of MM cases express increased cyclin D1 through biallelic dysregulation of *CCND1* and without apparent t(11;14); most of the remaining cases of MM, including those with t(4;14), have increased expression of cyclin D2. The expression level of cyclin D has also been incorporated into the molecular classification (Table 29.1).

### MicroRNA expression

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression at the post-transcriptional level and are involved in critical biological processes, including cellular growth and differentiation. Different studies have shown that miRNA expression is deregulated in myeloma cells as compared to normal plasma cells, and that their expression profile is associated with genetic abnormalities. Moreover, several miRNAs have been involved in MM pathogenesis. In this sense, it has shown a mechanism of p53 regulation through miRNAs acting on MDM2 expression; thus, miR-192, 194 and 215 re-expression in myeloma cell lines induce degradation of MDM2 with the subsequent p53 upregulation and cell growth inhibition.

### Multistep pathogenesis of multiple myeloma

The current pathogenic models assume that MM develops through a multistep transformation from normal plasma cells (PCs) to MGUS, which implies PC immortalization and, subsequently, the transformation to active MM, where clonal PCs cause end-organ damage. Cytogenetic studies using FISH have demonstrated that most genetic lesions typical of MM are already present at MGUS stage. We recently have shown that a major difference between these three entities is the number of PCs with genetic abnormalities, which increases from MGUS to SMM (smouldering multiple myeloma) and to MM, thus the progression from MGUS to SMM, and eventually to



**Figure 29.2** Interactions between plasma cells and the microenvironment. See text for definition of abbreviations.

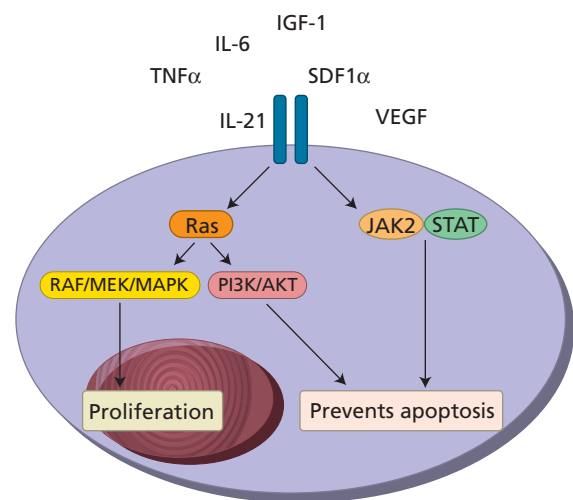
MM, involves a clonal expansion of genetically abnormal PCs. These findings have also been confirmed by SNP-based mapping arrays and whole-genome sequencing. Similarly, the progression of overt MM implies a complex evolutionary process with intra-clonal heterogeneity, where a Darwinian branching model drives a clonal competition with alternating dominance.

### Interaction between plasma cells and their microenvironment

As far as the pathogenesis of MM is concerned, interactions between the myelomatous plasma cells and their microenvironment can be as important as the genetic lesions. In the bone marrow, MM cells adhere to extracellular matrix proteins and bone marrow stromal cells through a series of adhesion molecules, for example the  $\beta_1$  integrin family (VLA-4, VLA-5, VLA-6; also called CD49d, CD49e and CD49f) (present in myeloma cells), and vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 (present in stromal cells) (Figure 29.2). In addition, bone marrow stromal cells produce a stromal-cell-derived factor (SDF)-1 that binds to CXCR4 on the surface of myeloma cells, inducing both chemotaxis of plasma cells and upregulation of surface adhesion molecules such as VLA-4. Bone marrow homing of plasma cells is likely further facilitated through other adhesion molecules expressed by myeloma cells, such as CD138, CD38, CD44 and CD106.

Adhesion of myeloma cells to the bone marrow microenvironment induces a cell adhesion-mediated drug resistance phenotype via three mechanisms: (i) cell cycle arrest at  $G_1$  (associated with upregulation of p27, an inhibitor of cyclin-dependent kinases), (ii) apoptosis inhibition via over-expression of FLIP-L, an endogenous inhibitor of FAS (CD95) and (iii) protection of tumour cells from initial drug-induced DNA damage

(double-strand breaks) by reducing topoisomerase II activity. The binding of MM cells to the bone marrow microenvironment also induces the transcription and secretion of cytokines, such as tumour necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, insulin-like growth factor (IGF)-1, IL-21, SDF-1 $\alpha$  and vascular endothelial growth factor (VEGF), by plasma cells and/or bone marrow stromal cells; this triggers signalling pathways (e.g. RAF/MEK/MAPK, PI3K/AKT, NF- $\kappa$ B and JAK/STAT) that promote cell proliferation and prevent apoptosis. These pathways are also potential targets for therapeutic intervention (Figure 29.3). In addition, cytokines modulate the production of additional adhesion molecules, which, in a vicious circle, further enhance cell adhesion.



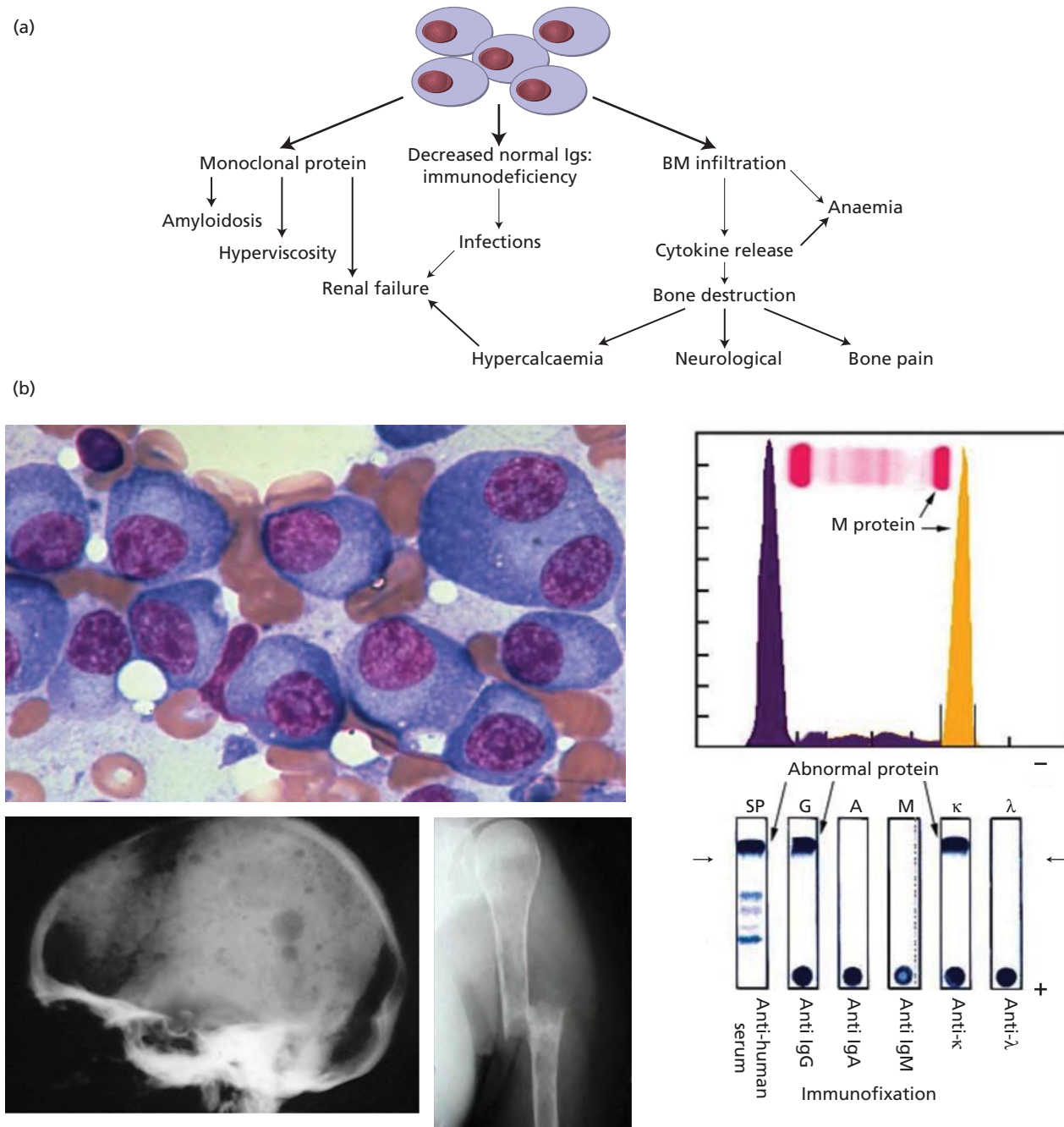
**Figure 29.3** Signalling pathways involved in myeloma pathogenesis. See text for definition of abbreviations.



In summary, it appears that the bone marrow microenvironment provides a sanctuary for myeloma cells by both promoting proliferation and blocking apoptosis, thereby allowing tumour progression and eventual emergence of drug resistance. Interruption by downregulating the interactions between the tumour cell and its microenvironment can potentially halt cell growth and proliferation and be of benefit to patients.

### Influence of pathogenesis on the clinical features of MM and the development of bone lesions

The interaction between MM cells and the microenvironment not only favours tumour growth, but is also responsible for the final myeloma portrait (see below and Figure 29.4). This



**Figure 29.4** (a) Clinical manifestations in myeloma and (b) bone marrow infiltration, monoclonal band (IgGκ by immunofixation) osteolytic lesions resulting in a pathological fracture.

interaction stimulates other cytokine cascades responsible for osteolytic lesions, which can result in bone pain, hypercalcaemia and neurological compression syndromes. Bone marrow infiltration also impairs normal haemopoiesis, leading to anaemia. MM cells secrete monoclonal protein (M-protein) that increases plasma viscosity. In addition, M-protein, and particularly light chains, are responsible for the impairment of renal function, leading ultimately to renal failure. Hypercalcaemia due to osteolytic disease may also contribute to renal failure. Patients are also at increased risk of developing potentially life-threatening infections due to the lack of functional immunoglobulins.

Bone disease is one of the hallmarks of MM (see below). Osteolysis is mediated by an imbalance between osteoclast activity (increased) and osteoblast activity (decreased). Interaction of MM cells with stromal cells and other cells in the microenvironment induces the secretion of numerous osteoclast-activating factors such as RANK-L, macrophage inflammatory protein (MIP)-1 $\alpha$  (also known as CCL3), activin A, VEGF, hepatocyte growth factor (HGF), IL-3, IL-7, TNF- $\alpha$ , IL-6, IL-1 $\beta$  and MIP-3 $\alpha$ . Two of the most important are RANK-L (receptor activator of NF- $\kappa$ B ligand) and MIP-1 $\alpha$ .

RANK-L is a transmembrane molecule in stromal cells/osteoprogenitors, which is also called TRANCE (TNF-related activation-induced cytokine) or OPG-L (osteoprotegerin ligand). RANK-L binds to its functional receptor RANK (TNF receptor superfamily) on osteoclasts, stimulating osteoclastogenesis by inducing differentiation of osteoclast precursors and stimulating resorption. RANKL activity can be blocked by osteoprotegerin (OPG), a soluble-decoy receptor for RANK-L also produced by stromal/osteoprogenitor cells. Therefore osteoclastic activity is regulated by a delicate balance between RANK-L and OPG. In fact, under normal physiological conditions, the levels of OPG are significantly higher than those of RANK-L. In contrast, in MM this balance is disrupted by increased expression of RANK-L and decreased expression of OPG on stromal cells after interaction with myeloma cells. It has been suggested that the decline in OPG is also mediated by myeloma cell uptake by binding to CD138 and subsequent degradation. MIP-1 $\alpha$  is a potent stimulator of osteoclast formation through a dual mechanism: (i) it enhances the activity of RANK-L and (ii) it directly stimulates osteoclast precursors to differentiate into mature forms. MIP-1 $\alpha$  gene expression is abnormally regulated in MM due to unbalanced expression of the acute myeloid leukaemia (AML)-1A and AML-1B transcription factors in myeloma cells. This imbalance also induces IL-3, which stimulates osteoclast formation and resorption directly or by further augmenting that of RANKL and MIP-1 $\alpha$ ; in addition, as mentioned below, IL-3 inhibits osteoblast formation. Other chemokines such as IL-7, TNF $\alpha$  and IL1 $\beta$  indirectly stimulate osteolytic processes, inducing RANK-L expression. Other OAFs secreted by myeloma cells and/or stromal/or osteoclasts cells (e.g. HGF, IL-6, VEGF, activin A), further increase the gradient

of osteoclastogenic factors in focal lesions and contribute to osteoclast production and activity.

In MM, in addition to the marked osteoclast activation, there is inhibition of osteoblast formation and function, which is mediated both by both soluble factors and direct cellular interactions of myeloma and stromal cells. The WNT/bone morphogenetic protein (BMP) signalling pathways are critical for the osteogenic differentiation of mesenchymal stem cells to mature bone-forming osteoblasts. Myeloma cells (and other BM microenvironmental cells) produce numerous soluble factors that inhibit osteoblast differentiation and/or function, such as Wnt signalling antagonists (e.g. DKK1, sclerostin, soluble frizzled related proteins (sFRP-2/3)), BMP inhibitors (e.g. activin A, TGF- $\beta$  and HGF), and other cytokines and chemokines (e.g. IL-7, TNF- $\alpha$  and IL-3 (which indirectly inhibits osteoblast differentiation involving CD45+ cells in the BM)). In addition, osteoblastic cells from myeloma patients with lytic lesions show reduced Runx2 activity, Runx2 being the major transcription factor regulating osteoblast differentiation. Suppression of Runx2 activity is mediated, at least in part, by cell-to-cell contact of myeloma and mesenchymal osteoprogenitors, since blocking of VLA4-VCAM1 interactions with a neutralizing anti-VLA4 antibody partially restored Runx2 function in mesenchymal cells.

## Differential diagnosis

The diagnostic criteria for the monoclonal gammopathies have been reviewed by the International Myeloma Working Group (IMWG). The main clinical entities are MGUS, primary systemic amyloidosis (see also Chapter 32), smouldering multiple myeloma and symptomatic multiple myeloma.

## Monoclonal gammopathy of undetermined significance

MGUS has a high prevalence (3.2% and 5.8% in individuals over 50 and 70 years of age, respectively). It is characterized by the presence of a serum M-protein (<30 g/L) and less than 10% plasma cells in the bone marrow with no evidence of other B-cell lymphoproliferative disorder and no symptoms or organ or tissue impairment due to the monoclonal gammopathy. The transformation rate to a malignant plasma cell disorder is about 1% per year, with an actuarial probability of malignant evolution of 30% at 25 years of follow-up. When the different causes of death are considered, the actuarial probability of malignant transformation at 25 years of follow-up is only 11%, much lower than the actuarial prediction. The main factors associated with MGUS progression include M-protein size, IgA isotype, abnormal free light-chain ratio and the 'evolving type' (rising M-protein during the first years of follow-up), and the presence of more than

95% phenotypically aberrant plasma cells within the bone marrow compartment.

When the proportion of bone marrow plasma cells is consistent with MGUS, but the patient has a nephrotic syndrome, congestive heart failure, peripheral neuropathy, orthostatic hypotension or massive hepatomegaly, the most likely diagnosis is primary systemic amyloidosis resulting from the deposition of amyloidogenic light chains. On the other hand, in a patient with constitutional symptoms, lytic bone lesions, a small M-spike and less than 10% plasma cells in the bone marrow, the most likely diagnosis is metastatic carcinoma with coincidental MGUS.

Smouldering multiple myeloma

The term ‘smouldering multiple myeloma’ (SMM) was first defined by Kyle and Greipp as the presence of a serum M-protein (>30 g/L) and 10% or more plasma cells in the bone marrow in the absence of lytic bone lesions or clinical manifestations due to the monoclonal gammopathy. More recently, the IMWG considered that the term ‘asymptomatic myeloma’ could be more appropriate. This condition was defined as the presence of an M-protein (≥30 g/L) and/or 10% or greater bone marrow plasma cells in the absence of symptoms or organ or tissue impairment due to the monoclonal gammopathy. About 10% of patients diagnosed with MM have smouldering disease. This situation is clinically and biologically very close to that observed in MGUS. However, the plasma cell mass is much higher and most cases will eventually evolve into symptomatic MM.

The annual risk of progression to symptomatic disease is 10% per year for the first 5 years, and it significantly decreases thereafter, 5% per year during the following 5 years and only 1% per year from the 10th year. SMM is not a uniform entity, since it includes from indolent, low-risk forms (that behave as MGUS) to ‘early myelomas’ at high risk of developing symptomatic diseases. This heterogeneous outcome is supported by the identification of risk factors predicting progression to symptomatic MM. The Mayo Clinic Risk Classification proposes three different subgroups of SMM: group 1 with ≥3 g/dL of MC and ≥10% of plasma cells in bone marrow, in which the median time to progression (TTP) to symptomatic MM is 2 years; group 2 with <3 g/dL of MC and ≥10% bone marrow plasma cells M-protein with a median TTP of 8 years and group 3 with ≥3 g/dL of MC, but with <10% plasma cells bone marrow infiltration, translating into a median TTP of 19 years. The Spanish group has proposed a risk classification based on the percentage of PCs with aberrant phenotype (high risk if ≥95% of the total PCs are clonal) plus immunoparesis (decrease in one or two of the uninvolved immunoglobulins), with a median TTP of 23 months when the two risk factors were present, as compared with 73 months when only one risk factor was present and not reached when none of the risk factors was present. Other adverse risk factors include an

Table 29.2 Myeloma-related organ or tissue impairment (end-organ damage) due to the plasma cell proliferative process.

<ul style="list-style-type: none"><li>• Increased serum calcium</li><li>• Renal insufficiency</li><li>• Anaemia: haemoglobin 20 g/L below the lowest normal limit</li><li>• Bone lesions: lytic lesions or osteoporosis with compression fractures (possibly confirmed by MRI or CT)</li><li>• Other: symptomatic hyperviscosity (rare), amyloidosis, recurrent bacterial infections (more than two episodes in 12 months), extramedullary plasmacytomas</li></ul>
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abnormal serum free light chain (FLC), evolving levels of para-protein, and cytogenetic abnormalities such as t(4;14), gain of 1q21 or hypodiploidy. Upon using either the Mayo or Spanish criteria, the high-risk SMM patients have a 70% risk of progression at 3 years. Moreover, more sensitive criteria can be used to identify patients at ‘ultra-high risk of progression’ (70% transform at 2 years): presence of FLC ratio ≥100, circulating PCs (>5 × 10<sup>6</sup>/L), more than 60% of BMPCs, focal lesions on spinal magnetic resonance. These patients should probably be considered as early myeloma and they would be candidates for early intervention. These risk stratification classifications may allow a more individualized disease management.

Symptomatic multiple myeloma

The diagnosis of symptomatic MM requires the presence of an M-protein in serum and/or urine, increased plasma cells in the bone marrow or plasmacytoma, and related organ or tissue impairment (including bone lesions). The more common symptoms are fatigue from anaemia and bone pain due to the skeletal involvement. Some patients may have no symptoms, but they can have related organ or tissue impairment. Clinical and laboratory features may include anaemia, skeletal involvement (lytic lesions and/or severe osteoporosis, with or without compression fractures), renal failure, hypercalcaemia, recurrent bacterial infections, extramedullary plasmacytomas or associated amyloidosis (Table 29.2). The criteria agreed by the IMWG for the diagnosis of symptomatic MM are shown in Table 29.3.

Table 29.3 Symptomatic multiple myeloma\*.

<ul style="list-style-type: none"><li>• M-protein in serum and/or urine</li><li>• Bone marrow (clonal) plasma cells or plasmacytoma<sup>†</sup></li><li>• Related organ or tissue impairment (end-organ damage, including bone lesions)</li></ul>
<p>*Some patients may have no symptoms, but have related organ or tissue impairment.</p> <p><sup>†</sup>If flow cytometry is performed, most plasma cells (&gt;90%) will show a ‘neoplastic’ phenotype.</p>



**Table 29.4** Laboratory work-up for a patient with monoclonal gammopathy.

- History and physical examination
- Complete blood count and differential peripheral blood film
- Chemistry including calcium and creatinine
- Serum protein electrophoresis and immunofixation
- Nephelometric quantification of immunoglobulins
- 24-hour urine collection for electrophoresis and immunofixation
- Bone marrow aspirate (cytogenetics, immunophenotyping and plasma cell labelling index if available)
- Radiological skeletal bone survey: CT or MRI may be helpful
- $\beta_2$ -Microglobulin, C-reactive protein and lactate dehydrogenase
- Measurement of free monoclonal light chains if available

Of note, no serum or urine M-protein values were included, since about 40% of patients with symptomatic MM have a serum M-protein level lower than 30 g/L and 3% have non-secretory myeloma. In the same sense, no minimal proportion of bone marrow plasma cells was required because about 5% of patients with well-documented symptomatic MM have less than 10% plasma cells in their bone marrow. Table 29.4 illustrates the laboratory work-up for patients with monoclonal gammopathies.

### Other special forms of plasma cell dyscrasia

#### Plasma cell leukaemia

Plasma cell leukaemia was initially described by Kyle in 1974 as a plasma cell disorder characterized by a relative peripheral blood plasmacytosis of more than 20% of total nucleated cells, or an absolute number of plasma cells greater than  $2 \times 10^9/L$ . It is likely that lower levels of circulating plasma cells (i.e.  $\geq 5\%$  and/or  $\geq 500 \times 10^9/L$ ) has a similar prognostic meaning. There are two forms of plasma cell leukaemia: the *de novo* presentation in leukaemic phase, and secondary cases corresponding to already diagnosed MM that evolve into a leukaemic phase. The clinical course of plasma cell leukaemia is usually very aggressive and resistant to conventional treatment and therefore new agents should be urgently investigated in these patients. A consensus statement on the diagnostic criteria and treatment approach by the International Myeloma Working Group has been recently published.

#### Solitary plasmacytoma of bone

The existence of a solitary plasmacytoma has been recognized in up to 3% of patients with a plasma cell dyscrasia, usually on the vertebral column. The diagnostic criteria require the existence

of a solitary plasma cell tumour in which the biopsy confirms plasma cell histology, a negative skeletal survey and absence of plasma cell infiltration in a random bone sample ( $<10\%$ ), as well as no evidence of anaemia, hypercalcaemia or renal impairment. Some groups suggest that patients in whom a paraprotein persists after the eradication of plasmacytoma with local treatment should undergo a review of the diagnosis. The treatment of choice is local radiotherapy, but about two-thirds of patients with solitary bone plasmacytoma develop MM at 10 years' follow-up, with a median time to progression of 2 years.

#### Extramedullary plasmacytoma

Extramedullary plasmacytoma is a plasma cell tumour that arises outside the bone marrow, most frequently in the upper respiratory tract (nose, paranasal sinuses, nasopharynx and tonsils). Other sites include parathyroid gland, orbit, lung, spleen, gastrointestinal tract, testes and skin. In most cases the lesion is unique, although the presence of more lesions (multiple plasmacytomas) has also been reported. Diagnosis is based on the detection of the plasma cell tumour in an extramedullary site, in the absence of bone marrow plasma cell infiltration, bone lytic lesions and other signs of MM (end-organ damage).

#### Non-secretory multiple myeloma

This specific type of MM requires particular attention, since it is very difficult to diagnose. The only way to make a definitive diagnosis is to demonstrate the presence of tissue infiltration (usually bone marrow) by cells with plasma cell morphology. However, plasma cell infiltration must be greater than 10% and clonality must be assessed by immunophenotyping (demonstration of cytoplasmic immunoglobulins with restricted light chain: positive production without excretion). In addition, the serum free light chains are abnormal and this is a most useful parameter for the follow-up. However, exceptional cases exist in which no monoclonal protein can be observed within the plasma cells. In these cases, it is mandatory to demonstrate clonality by the study of the rearrangement status of the immunoglobulin genes.

#### IgM multiple myeloma

This exceptional form of myeloma has been reported very rarely and must be distinguished from Waldenström macroglobulinaemia. The morphology and immunophenotype of the infiltrating cells will give the definitive diagnosis, as well as the existence of osteolytic lesions, which are absent in Waldenström macroglobulinaemia.

#### Osteosclerotic myeloma (POEMS syndrome)

POEMS syndrome is characterized by polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes. The clinical picture consists of a chronic inflammatory

demyelinating polyneuropathy, more motor than sensory, and osteosclerotic lesions. Hepatomegaly, hyperpigmentation, hypertrichosis, angiomatous lesions on the trunk, gynecomastia, testicular atrophy and papilloedema or thrombocytosis may occur. The M-protein is commonly of IgA  $\lambda$  type and the bone marrow contains less than 5% plasma cells. Castleman disease can be associated and VEGF is universally increased. Biopsy of an osteosclerotic lesion may be necessary to confirm the diagnosis. Mandatory diagnostic criteria are the presence of an M-protein and polyneuropathy, and major criteria are the presence of osteosclerotic lesions, Castleman disease and elevated VEGF. At least the two major criteria plus one major finding and a minor clinical criteria (above mentioned) are necessary for diagnosis.

Amyloid disease is dealt with in Chapter 30.

### Disease complications and their management

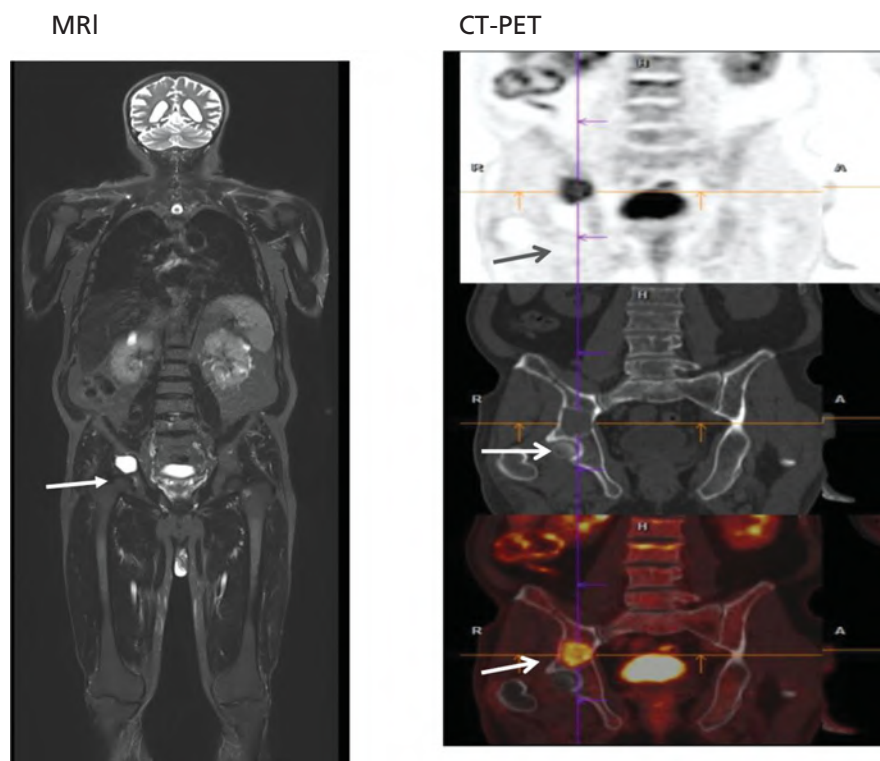
Figure 29.4 illustrates the clinical manifestations of multiple myeloma.

#### Bone involvement: assessment and treatment

Bone involvement is the most frequent clinical complication in patients with MM. About 70% of patients have lytic bone

lesions, with or without osteoporosis, and another 20% have severe osteoporosis without lytic lesions. This frequency corresponds to conventional skeletal radiography assessment, a technique that is associated with low sensitivity (only demonstrating lytic disease when at least 30% of bone substance has been lost), particularly in some areas (ribs, sternum), low specificity (gas in colon) and long examination time. However, it has two major advantages: is widely available and remains as the international standard (for CRAB criteria). Newer imaging techniques have greater sensitivity compared with radiographic bone survey for detection of MM bone lesions (Figure 29.5). Computed tomography (CT) has the highest sensitivity for the detection of bone defects and with the whole-body low-dose modality the radiation exposure is much lower than with conventional CT, the scanning time is short and it may replace conventional X-ray in the near future. Magnetic resonance imaging has the highest resolution for soft tissue and bone marrow infiltration; it is particularly valuable for differentiation between benign and malignant fractures, but is inferior to CT for assessment of bone disease. Finally, positron emission tomography (PET) allows assessment of tumour metabolism and disease activity (versus inactive or necrosis), and may be of prognostic significance; however, it still requires great work on standardization.

These new techniques are already recommended to evaluate patients with SMM and solitary plasmacytoma, and although up until now the presence of one or more clear sites of osteolytic bone destruction seen on CT and/or PET-CT does fulfill the



**Figure 29.5** MRI and PET/CT in a myeloma patient. The arrows show a myeloma lesion in the lower part of the right iliac bone. The T2 weighted MRI shows a hyperintense image (left) and an active lesion at FDG PET/CT is confirmed (right).

CRAB criteria, the situation will probably change soon. Nevertheless, great caution should be paid to avoid over-interpretation of equivocal or tiny lucencies seen only on CT or PET-CT.

From the clinical point of view, the skeletal involvement leads to bone pain and can result in pathological fractures. The pathophysiology of bone disease has been described above. Some patients develop pathological fractures of long bones and require orthopaedic surgery. In the event of extensive lesions, surgery can be followed by radiation therapy. On the other hand, prophylactic orthopaedic intervention must be considered in patients with large lytic lesions at high risk of fracture. It is important to consider that patients with severe back pain due to vertebral compression fractures can benefit from vertebroplasty or kyphoplasty. Spinal cord compression caused by a vertebral fracture is very rare in patients with MM. This complication is usually caused by a plasmacytoma arising from a vertebral body.

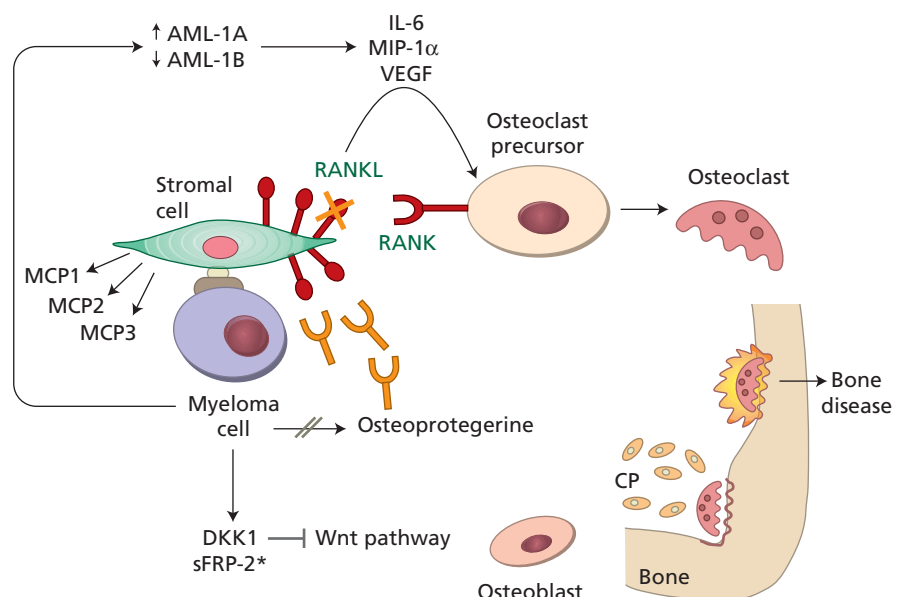
Between 15 and 20% of patients with MM have hypercalcaemia at the time of diagnosis. A common complication of hypercalcaemia is renal impairment caused by interstitial nephritis. Treatment of hypercalcaemia with hydration and bisphosphonates is a medical emergency. Zoledronic acid is the bisphosphonate of choice (quicker response and significantly longer time to recurrence compared with pamidronate).

The intravenous agents pamidronate and zoledronic acid are of clinical benefit in the treatment of bone disease in patients with MM. Pamidronate is administered at a monthly dose of 90 mg via a 2-hour intravenous infusion. Zoledronic acid, at a monthly dose of 4 mg, is at least as effective as pamidronate and has the advantage that it can be administered via a 15-min infusion. In patients with renal function impairment, the dose of zoledronic acid must be reduced to a maximum of 3 mg. It was

suggested that bisphosphonates should be used indefinitely, once initiated. However, the appearance of severe late complications, such as osteonecrosis of the jaw, related to the duration of bisphosphonate exposure has resulted in a reconsideration of the initial recommendations. Osteonecrosis of the jaw is associated with the duration of bisphosphonate exposure, type of bisphosphonate (higher with zoledronic acid than with pamidronate) and history of recent dental procedure. The current recommendations for treatment with bisphosphonates in MM patients, based on consensus panels from both the IMWG and the ASCO, do not recommend the initial use of bisphosphonates for more than 2 years. In relapsed patients, treatment with bisphosphonates can be re-started and administered concomitantly with active therapy. Finally, in patients in whom the bone disease is a consequence of excess RANK-L activity, newer molecules such as denosumab might be of benefit. The pathogenesis of myeloma bone disease is summarized in Figure 29.6.

## Renal failure

About 20% of patients with MM have a serum creatinine higher than 177  $\mu\text{mol/L}$  (2 mg/dL) at diagnosis. The degree of renal failure is usually moderate, with a serum creatinine lower than 354  $\mu\text{mol/L}$  (4 mg/dL). However, in some series up to 10% of patients with newly diagnosed MM have renal failure severe enough to require dialysis from the time of diagnosis. The main causes of renal failure in MM are: (i) light-chain excretion resulting in cast nephropathy (myeloma kidney) and (ii) glomerular deposition of immunoglobulin (light-chain amyloidosis or immunoglobulin deposition disease). In myeloma kidney, the typical feature consists of the presence of myeloma casts, mainly composed of light chains, in the distal tubules and



**Figure 29.6** Pathogenesis of bone disease. See text for definition of abbreviations.

collecting ducts. There is a correlation between the degree of cast formation and the severity of renal failure. Light-chain tissue deposition usually consists of glomerular deposits of immunoglobulins, resulting in nephrotic syndrome. The amyloid deposits are fibrillar structures of light chains showing positive Congo red staining. In light-chain deposition disease, the deposit of light-chain immunoglobulins is non-fibrillar (Congo red negative). In contrast with amyloidosis, the light chain is usually of the  $\kappa$  type. The characteristic clinical feature is a nephrotic syndrome, but renal function can rapidly deteriorate, resembling glomerulonephritis (see also Chapter 30).

The median survival of patients with MM and renal insufficiency is less than 1 year. However, the prognosis mainly depends on the reversibility of renal function. Thus, the median survival of patients with reversible renal failure is similar to that of patients with normal renal function, whereas patients with non-reversible renal failure have a median survival of less than 6 months. The factors associated with renal function recovery include serum creatinine lower than 354  $\mu\text{mol/L}$  (4 mg/dL), 24-hour urinary protein excretion lower than 1 g, and serum calcium higher than 2.875 mmol/L (11.5 mg/dL).

Vincristine, doxorubicin (Adriamycin) and high-dose dexamethasone (VAD), or cyclophosphamide and dexamethasone, or even dexamethasone alone, in very frail patients, appear to be better approaches than melphalan-containing regimens because of both lower myelosuppression and quicker action. The novel drugs introduced for myeloma treatment are of great value in patients with renal failure. Taking into account that the action of bortezomib is very quick, it is probably an ideal agent for rapidly decreasing light chains in order to prevent the development of irreversible renal failure by avoiding further tubular light-chain damage. In a retrospective series of 24 patients with relapsed/refractory MM and dialysis-dependent renal failure, the overall response rate (RR) was 75%, with 30% complete remissions (CR) or near-CR. Recent studies have confirmed the benefit of bortezomib-based therapies in patients with newly diagnosed myeloma and renal failure. The association of lenalidomide and dexamethasone could also be a good treatment option for patients with renal failure. However, the dose of lenalidomide must be adjusted to the degree of renal failure according to the guidelines for the use of lenalidomide in patients with renal function impairment.

With regard to the use of high-dose therapy/autologous stem cell transplantation (SCT) in patients with MM and renal failure, the largest experience comes from the Arkansas group, with a reversibility of renal failure of 43%, but higher morbidity and mortality (6% and 13% after a single or tandem transplant, respectively) than in patients with normal renal function. Chemoresistant disease, low serum albumin and older age were associated with a poorer outcome. In any event, the dose of melphalan must be reduced to 140 mg/m<sup>2</sup>. In patients with no overt myeloma and low plasma cell mass in whom renal function impairment is due to glomerular light-chain deposition (light-

chain deposition disease), the likelihood of response is higher than that in MM because of the low plasma cell mass at the time of transplantation. In this situation there is no need for tumour reduction with induction chemotherapy before stem cell mobilization and high-dose therapy.

Theoretically, the removal of nephrotoxic light chains with plasma exchange could avoid further renal failure and hopefully prevent irreversible renal failure. The Mayo Clinic group, in a small controlled trial, compared chemotherapy with chemotherapy plus plasma exchange and found only a trend in favour of the group including plasma exchange. Similarly, in a large randomized trial there was no conclusive evidence that plasma exchange improved the outcome of patients with MM and acute renal failure. When excluding the patients who die in this early period, the median survival of patients with MM and non-reversible renal failure needing chronic dialysis is almost 2 years and 30% of them survive for more than 3 years. Thus, long-term dialysis is a worthwhile supportive measure for patients with MM and end-stage renal failure. The use of high cut-off dialysis filters is very promising and hopefully prospective ongoing studies will confirm its benefit.

## Anaemia and bone marrow failure

Approximately 35% of patients with newly diagnosed MM have a haemoglobin level lower than 90 g/L. In addition, severe anaemia is a frequent complication later in the course of the disease due to disease progression. Anaemia is associated with a significant loss in quality of life and poor prognosis. The main causes of anaemia in MM are bone marrow replacement by plasma cells, relative erythropoietin deficiency, renal insufficiency and chemotherapy with cytotoxic agents.

Severe granulocytopenia and thrombocytopenia at the time of diagnosis are unusual. About 10% of patients have a platelet count of less than  $100 \times 10^9/\text{L}$ , but platelet counts lower than  $20 \times 10^9/\text{L}$  with risk of severe bleeding are very unusual. The development of an unexplained pancytopenia in patients previously treated with alkylating agents, particularly melphalan, is suspicious of myelodysplasia.

A number of trials have shown the beneficial effect of recombinant human erythropoietins and darbepoetin- $\alpha$  in the treatment of myeloma-associated anaemia. The response to erythropoietin is associated with a significant improvement in quality of life. An important aspect is that the most significant improvement in quality of life is reached when the haemoglobin increases from 110 to 120 g/L, but levels above 140 g/L should be avoided due to its association with a higher risk of thrombosis. Thus, the goal should be maintenance of the haemoglobin around 120 g/L, with careful dose titration in order to achieve a good quality of life, while minimizing severe complications such as thrombotic events. The major cause of erythropoietin failure is iron deficiency. Iron repletion should be indicated when there is evidence of functional iron deficiency measured by an



increased soluble transferrin receptor. It seems that the best iron supplemental therapy is the administration of iron saccharate. Treatment with granulocyte colony-stimulating factor (G-CSF) may be required to treat chemotherapy-induced severe granulocytopenia. Patients treated with lenalidomide may require G-CSF therapy.

## Infection

Infectious complications are the major cause of morbidity and mortality in patients with MM. The highest risk of infection is observed during the first 2 months of starting therapy, in patients with severe chemotherapy-induced granulocytopenia and in those with relapsed and refractory disease. The main cause of infection in MM is the impaired antibody production, leading to a decrease in the uninvolved immunoglobulins. Other important causes include chemotherapy-induced granulocytopenia, renal function impairment and glucocorticoid treatment, particularly high-dose dexamethasone. Most infections in newly diagnosed patients and during the first cycles of chemotherapy are caused by *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae*, while in patients with renal failure, as well as in those with relapsed and/or refractory advanced disease, more than 90% of the infectious episodes are caused by Gram-negative bacilli or *Staph. aureus*.

An infectious episode in a patient with MM should be managed as a potentially serious complication requiring immediate therapy. In case of suspected severe infection and before the identification of the causal agent, treatment against encapsulated bacteria and Gram-negative microorganisms should be initiated. Although prophylaxis of infection in patients with MM is a controversial issue, some general guidelines can be offered. Intravenous immunoglobulin prophylaxis is not recommended. Pneumococcal vaccination is recommended, particularly in patients with IgG myeloma with high-serum M-protein levels, which are usually associated with very low levels of uninvolved immunoglobulins. Antibiotic prophylaxis is likely of benefit within the first 2 months of initiation of therapy, especially in patients at high risk of infection (recent past history of serious infections, such as recurrent pneumonia, or renal failure). Patients treated with bortezomib should receive prophylaxis against varicella-zoster infections.

## Nervous system involvement

Spinal cord compression from a plasmacytoma, which occurs in about 10% of patients, is the most frequent and serious neurological complication in MM. The dorsal spine is the most common site of involvement, followed by the lumbar region. The clinical picture of spinal cord compression consists of back pain and paraparesis. Although it can evolve for several days or even a few weeks, the onset can be abrupt, resulting in severe paraparesis or paraplegia in a few hours. The picture is usually accompanied by

a high sensitivity level. Lumbar involvement can cause a cauda equina syndrome (low back pain with radicular distribution and leg weakness).

Spinal cord compression is an emergency requiring immediate medical action. When suspected, urgent magnetic resonance imaging (MRI) should be performed. If confirmed, treatment with high-dose dexamethasone must be started immediately at a loading dose of 100 mg, followed by 25 mg every 6 hours, followed by progressive tapering. Simultaneous local radiation therapy should be started as soon as possible. If the spinal cord compression is caused by a vertebral collapse or by spinal instability rather than a plasmacytoma (which is very rare), urgent surgical decompression followed by fixation of a prosthesis of bone graft or methacrylate is required.

Nerve root compression can cause back pain that follows a radicular metameric distribution with or without radicular sensory involvement. Treatment with radiation therapy is helpful, allowing time for the action of systemic chemotherapy. Clinically significant peripheral neuropathy (PN) is very uncommon in newly diagnosed patients with MM. Leptomeningeal involvement in the central nervous system (CNS) with detection of plasma cells in the cerebrospinal fluid (CSF) is exceedingly rare. The frequency of CNS involvement is roughly 1%, the most frequent presenting features being paraparesis, symptoms from increased intracranial pressure, cranial nerves palsies and confusion. The CSF examination frequently shows plasma cells of plasmablastic morphology, as well as an increased protein concentration with positive immunofixation for the myeloma protein. Unfortunately, despite active treatment measures such as intrathecal therapy (methotrexate, cytarabine, glucocorticoids), cranial or even craniospinal irradiation, the prognosis is extremely poor with a median survival of 3 months from the diagnosis of CNS involvement.

## Prognostic factors

The outcome for patients with MM is highly heterogeneous, with survival duration ranging from a few months to more than 10 years. This heterogeneity relates to: (i) specific characteristics of the tumour itself, (ii) host factors and (iii) a series of factors resulting from the interaction between the tumour clone and the host, which mainly reflect tumour burden and disease complications (Table 29.5).

## Host factors

The favourable influence of a good performance status (ECOG  $\geq 2$ ) and young age (<65–70 years) is well established. In contrast, neither sex nor race has prognostic influence. Immune surveillance, by T and natural killer (NK) cells, plays a relevant role in most malignancies, and low numbers of



**Table 29.5** Prognostic factors in MM.

Prognostic factors	Tumour related	Host related	Tumour burden
Essential	Cytogenetics/FISH: t(4;14), t(14;16), 17p deletions, 1q gains, 1p deletions	Age	International Staging System ( $\beta_2$ -microglobulin/albumin)
Additional	Hypodiploidy LDH Plasma cell proliferation Immunophenotyping markers	Performance status	
New and promising	DNA copy number abnormalities by SNP arrays	Immune status	Circulating clonotypic plasma cells sRANK-L

mature NK and CD4 cells have been reported in advanced-stage MM. In addition, patients who develop expanded T-cell clones (CD8+CD57+CD28–), which can recognize autologous idiotypic immunoglobulin structures, display favourable outcome.

### Malignant clone factors

The second cohort of prognostic factors are those that reflect specific characteristics of myelomatous plasma cells and include morphology, immunophenotyping, cytogenetics, oncogenes, multidrug resistance and proliferative activity of plasma cells. Immature/plasmablastic morphology is associated with poor outcome. With regard to antigen expression, we have observed that downregulation of CD117 (c-Kit) and CD56, and expression of CD28 and CD19, are associated with poor prognosis. As occurs with acute leukaemia, cytogenetic abnormalities are the most important prognostic markers for MM. Nowadays, cytogenetic evaluation is mandatory in all patients with newly diagnosed MM, and should always include FISH in purified PCs or in combination with immunofluorescent detection of light-chain-restricted PCs (cIg-FISH). Among *IGH* translocations, patients with t(4;14) treated with either conventional or intensive chemotherapy display shorter event-free survival and overall survival. However, recent analysis supports the notion that patients with t(4;14) make up a heterogeneous group. Thus, the French group has discriminated a subgroup of these patients (approximately 45%) with both low  $\beta_2$ -microglobulin and high haemoglobin levels at diagnosis, which displays prolonged survival after tandem transplant and benefits from high-dose therapy. The association of t(14;16) with prognosis has not been well supported because of its low frequency. According to Mayo Clinic data, t(14;16) was linked to poor outcome in the context of conventional chemotherapy. However, controversial results have been reported using autologous transplant: the IFM group did not confirm the poor prognostic value of t(14;16) in patients receiving a tandem-autologous transplantation approach, whereas a recent study from the MRC showed a significantly shorter survival among patients with t(14;16)

treated with autologous transplant. In contrast to t(4;14) and t(14;16), the presence of t(11;14) was shown to have either a favourable or an irrelevant influence on prognosis. Initial studies indicated that monosomy 13/del(13) was associated with poor outcome; however, analyses based on large series of MM patients have revealed that the presence of monosomy 13/del(13) as a unique abnormality, without concomitant *IGH* abnormalities, is not indicative of unfavourable prognosis. In contrast, del(17p) (with deletion of the *TP53* gene) is one of the most, if not the most, adverse prognostic factor in MM. It seems that the higher the proportion of PCs bearing 17p deletions, the shorter the survival. Several studies have shown that 1q gains have a significant and independent poor prognostic factor; in addition, the IFM group has reported that 1p deletions are a major independent prognostic factor. Moreover, the presence of complex, as well as non-hyperdiploid karyotypes also predict treatment failure. In contrast, hyperdiploid tumours with multiple trisomies involving chromosomes 3, 5, 7, 9, 11, 15, 19 and 21 tend to have a favourable prognosis. In line with this latter observation, we have shown that patients with hyperdiploid DNA cell content (defined by flow cytometry) have a favourable outcome. Finally, the proliferative activity of the malignant plasma cells, as assessed either by the labelling index with bromodeoxyuridine or by flow cytometry, is one of the most important prognostic markers.

One of the aims of cytogenetic classification is to define a high-risk group that should be managed differently from standard-risk patients. According to IMWG recommendation, the term 'high-risk MM' should include those patients with at least one of the following features: deletion of 17p, t(4;14) or t(14;16), detected by FISH analysis. Hypodiploidy defined by karyotyping is also used by the Mayo Clinic to define high-risk patients. Recently, a prognostic model in MM based on the frequently associated genetic lesions has been proposed. Accordingly, three genetic risk groups were defined: a favourable risk group with no adverse FISH lesions, an intermediate group with one adverse genetic lesion – t(4;14), t(14;16) or t(14;20); 17p deletion or 1q gain – and a high-risk group with more than one adverse genetic lesion.

## Tumour burden and disease complications

A high proportion of plasma cells in the bone marrow, diffuse bone marrow infiltration and the presence of circulating plasma cells reflect a high tumour burden, but their prognostic influence is modest. Similarly, the impact of skeletal lesions, evaluated by radiography or bone resorption markers, is not clear. In contrast, disease complications such as anaemia, thrombocytopenia and particularly renal insufficiency have a major influence. Nevertheless, the most important factor is the concentration of  $\beta_2$ -microglobulin, which increases as a result of both growth of tumour burden and deterioration in renal function. The higher the value, the worse the prognosis. Nevertheless,  $\beta_2$ -microglobulin is not helpful for disease monitoring. C-reactive protein is a surrogate marker for IL-6 (a major plasma cell growth factor), which also correlates with outcome. In contrast to hypoalbuminaemia, neither the amount of paraprotein nor its isotype influences prognosis.

Only a few of the prognostic factors have real independent value. A summary of the most important is shown below:

- 1 Two host factors (*age* and *performance status*) reflect the ability of the patient to tolerate chemotherapy
- 2 Two intrinsic characteristics of the malignant clone (*cytogenetics* and *plasma cell proliferative activity*)
- 3 One biochemical marker that reflects tumour burden ( $\beta_2$ -microglobulin).

The International Staging System (ISS), derived from more than 11,000 patients, has shown that  $\beta_2$ -microglobulin and albumin are the best combination of easily available markers for discriminating prognostic subgroups: stage I ( $\beta_2$ -microglobulin  $<3.5$  mg/dL, albumin  $>3.5$  mg/dL); stage III ( $\beta_2$ -microglobulin  $>5.5$  mg/dL); stage II (the rest). This substitutes for the Durie and Salmon classification, which affords little prognostic information. In the next few years, improved staging systems using cytogenetics and S-phase analysis should be developed for use by reference centres and eventually for all patients with myeloma.

## Response to therapy as a prognostic factor

In addition to all the variables that can be measured at diagnosis and which have already been mentioned, response to front-line therapy represents one of the most important prognostic factors in most haematological malignancies. In the case of MM there is still open debate about the importance of the depth of response on patient outcome. The reason for this controversy is probably that, historically, until the introduction of high-dose chemotherapy, CR was extremely rare and the only available comparison was between responding patients (achieving partial or minor responses) and non-responding patients, with the former having a better outcome. A recently published meta-analysis, including 21 reports with independent datasets for which outcome data were reported, has shown a very significant association between

the maximal response obtained after treatment and the two main long-term-outcome parameters, i.e. overall survival (OS) and time to progression-related events. However, it is clear that more sensitive techniques (e.g. multiparametric immunophenotyping, molecular analysis of bone marrow plasma cells by PCR, serum free light-chain test and imaging techniques such as MRI or PET to detect myeloma activity outside the bone marrow) are needed to evaluate response in MM and these may contribute to a better assessment of the impact of response in final outcome. Both the Spanish and UK groups have shown that when transplanted and elderly MM patients show undetectable residual myelomatous plasma cells by immunophenotyping, progression-free survival (PFS) and OS are significantly longer, and this parameter is significantly more powerful than negative immunofixation.

## Criteria of response

Response criteria were initially developed by the Chronic Leukaemia and Myeloma Task Force (CLMTF) in 1968. The main response parameter was a minimum 50% reduction in the M-protein. In 1972 the Southwest Oncology Group (SWOG) defined partial response (PR) as a reduction of at least 75% in the calculated serum paraprotein synthetic rate and/or a decrease of at least 90% in urinary light-chain urine protein excretion sustained for at least 2 months. The Medical Research Council (MRC) introduced the concept of plateau phase, defined as a period of stability after chemotherapy in which tumour progression does not occur, despite the presence of measurable disease. The minimum period of stability required for definition of plateau phase was 3 months. Since CRs were rarely observed with the classical conventional dose chemotherapy, neither the CLMTF nor the SWOG response criteria included a definition of CR. In addition there were no definitions for relapse and progression.

## EBMT criteria for response, relapse and progression

With the introduction of high-dose therapy/SCT, the M-protein disappears in a significant number of patients, a fact that is associated with a significant prolongation of survival. In this context, the European Group for Blood and Marrow Transplantation (EBMT) developed new criteria defining CR (negative immunofixation in serum and urine and less than 5% bone marrow plasma cells), PR ( $\geq 50\%$  reduction in serum M-component and  $\geq 90\%$  in 24-hour urine Bence-Jones proteinuria) and minimal response (MR) (25–49% decrease in M-component), as well as criteria for relapse (reappearance of M-protein by immunofixation in patient who had achieved CR, and progression from PR or MR). Any type of response should be maintained for a minimum of 6 weeks. These criteria have been shown to be useful and reproducible in both transplant and non-transplant series, as well as in prospective clinical trials.

**Table 29.6** International uniform response criteria for multiple myeloma (IMWG response criteria).

Response category*	Criteria
Complete remission (CR)	Negative immunofixation (serum and urine) <5% bone marrow plasma cells No soft tissue plasmacytomas
Stringent CR	As above, <i>plus</i> Normal free light-chain ratio Absence of clonal plasma cells <sup>†</sup>
Very good partial response	≥90% decrease in serum M-protein Urine M-protein <100 mg per 24 hours
Partial response	≥50% decrease in serum M-protein ≥90% decrease in urine M-protein or <200 mg per 24 hours ≥50% decrease in soft tissue plasmacytomas

\*All response categories require two consecutive measurements made at any time.

<sup>†</sup>Determined by immunohistochemistry or immunofluorescence.

### Uniform response criteria

The IMWG has expanded the EBMT criteria by adding the categories of stringent CR (sCR) and very good partial response (VGPR) (Table 29.6). Patients with negative immunofixation in serum and urine and with a normal free light-chain ratio are considered in sCR. The free light-chain measurement has also been included for the evaluation of response in patients with non-secretory and oligosecretory disease. VGPR requires a decrease in the M-protein size of at least 90%. In addition, time to event, duration of response, clinical relapse and time to alternative therapy are emphasized as critical end points. More recently, the IMWG has considered the possibility of also adding the parameters 'CR by immunophenotyping' and 'CR by molecular techniques', as well as the reintroduction of minor responses for treatment evaluation of relapse/refractory patients.

## Treatment

In this section we focus on the treatment of the malignant clone, since the management of disease complications (anaemia, renal insufficiency, bone disease) has been discussed above.

Melphalan–prednisone (MP) was introduced for the treatment of MM in the late 1960s. In the subsequent 30 years, treatment improvements remained stagnant, since more complex chemotherapy combinations (e.g. VCMP, VBAD, VAD)

only led to small increases in the overall RR, but without differences in survival, as assessed in a large meta-analysis that included over 6000 patients. The next step forward was the use of high-dose melphalan followed by stem cell support (autologous SCT) for young myeloma patients, which resulted in a significant improvement in disease-free survival and OS. However, for elderly patients, MP remained the standard of care. From 2000, there was a revolution in the treatment of MM with the availability of new agents with distinct mechanisms of action: the immunomodulatory drugs thalidomide and lenalidomide (Revlimid) and the proteasome inhibitor bortezomib (Velcade).

In this section we first discuss the treatment of newly diagnosed patients stratified according to age (above or below 65–70 years), which categorizes the patients as transplant or non-transplant candidates, and then analyse the options for relapse/refractory patients, as well as emerging novel agents.

### Should all myeloma patients be treated?

Currently, only myeloma patients with symptomatic disease (defined by CRAB criteria) should be treated, patients with smouldering myeloma are not treated until they develop symptomatic disease. Attempts at early intervention in SMM patients with alkylating agents, bisphosphonates, antagonists of the receptor of interleukin 1 $\beta$  or thalidomide failed to show a significant benefit; however, none of these studies discriminated between high- and standard- or low-risk SMM patients. By contrast, the Spanish group has conducted a Phase III randomized trial focusing on high-risk smouldering myeloma patients, comparing early treatment with lenalidomide–dexamethasone induction therapy followed by lenalidomide maintenance therapy versus observation. The results showed that the experimental arm was associated with a significant delay in progression to symptomatic myeloma (3 years after study entry, 77% of patients in Group A and 30% in Group B were progression-free; hazard ratio, 5.59;  $P < 0.001$ ). This delay translated into a significant overall survival benefit (the proportions of patients alive at 3 years was 94% and 80%, respectively; hazard ratio, 3.24;  $P = 0.03$ ). Although, these data suggest a benefit for early intervention in high-risk SMM patients, other trials are needed before this becomes a new standard of care. Moreover, ongoing efforts are trying to better define the high-risk population.

### Treatment of newly diagnosed transplant candidate patients

Currently, treatment in this setting usually includes three to six cycles of induction therapy, followed by autologous SCT and the possibility of consolidation and maintenance.

#### Induction

The VAD combination has long been the gold standard as a preparatory regimen for young newly diagnosed MM patients

**Table 29.7** Response to induction treatment in transplant candidate patients: results from Phase III front-line trials\*.

Regimen	Patients	PR or better (%)	CR + n-CR (%)	Study
TD versus D	470	63 versus 46	7 versus 2.6	Rajkumar <i>et al.</i> (2008)
TD versus VAD	200	76 versus 52	10 versus 8	Cavo <i>et al.</i> (2005)
TAD versus VAD	400	–	35 versus 13	Macro <i>et al.</i> (ASH 2006)
TVAD versus VAD	230	81 versus 66	–	Zervas <i>et al.</i> (2007)
CTD versus CVAD	1161	87 versus 75	13 versus 8	Morgan <i>et al.</i> (ASH 2012)
BD versus VAD	482	80 versus 63	21 versus 8	Harousseau <i>et al.</i> (2010)
BTD versus TD	256	93 versus 74	36 versus 9	Cavo <i>et al.</i> (2010)
LD <sub>high</sub> versus LD <sub>low</sub> <sup>†</sup>	445	82 versus 71	4 versus 2	Rajkumar <i>et al.</i> (2010)
LD versus D	198	85 versus 51	22 versus 4	Zonder <i>et al.</i> (ASH 2007)
BTD versus TD	257		35 versus 14	Rosin�ol <i>et al.</i> (2012)
PAD versus VAD	827		7 versus 2	Sonneveld <i>et al.</i> (2012)

\*Response after autologous SCT (CR + n-CR): TAD versus VAD (16% versus 11%); CTD versus CVAD (51% versus 39%); BD versus VAD (35% versus 24%); BTD versus TD (57% versus 28%), BTD versus TD (46% versus 24%), PAD versus VAD (21% versus 5%), CTD versus CVAD (33% versus 25%)

\*High-dose dexamethasone (three pulses), low-dose dexamethasone (one pulse).

<sup>†</sup>A, Adriamycin; B, bortezomib; D, dexamethasone; L, lenalidomide; T, thalidomide; V, vincristine; CR, complete remission; n-CR, near complete remission; ASH, American Society of Hematology (Annual Meeting).

who are candidates for autologous SCT, with PR rates ranging from 52 to 63% and CR rates from 3 to 13%. However, novel drug combinations are superior to VAD-like regimens for decreasing tumour burden before transplantation. As shown in Table 29.7, three randomized trials have compared thalidomide (T)-based regimens (TD or TAD or TVAD) versus either high-dose dexamethasone or VAD as initial therapy in transplant-eligible patients. In all studies, thalidomide combinations were superior to conventional induction treatment, although the response rate (PR or greater) obtained with thalidomide plus dexamethasone (63%) was lower than that achieved with TAD or TVAD (80%, with CR rates usually <10%). The MRC group has compared cyclophosphamide (C) plus thalidomide and dexamethasone with CVAD as an induction regimen before transplantation; the thalidomide arm was significantly superior (RR 87% versus 75%; CR 20% versus 12%). In studies evaluating bortezomib (B) combination therapy, data from a French randomized trial that compared bortezomib plus dexamethasone with VAD show the superiority of bortezomib plus dexamethasone, both before and after transplantation (Table 29.7). The Italian group has shown the superiority of bortezomib, thalidomide and dexamethasone over thalidomide and dexamethasone (Table 29.7). The high efficacy of bortezomib-based regimens as induction treatment is consistent with several pilot studies using either bortezomib plus dexamethasone alone or in combination with doxorubicin (Adriamycin/Doxil) or thalidomide, with RRs usually over 80% and CR rates of 18–32%. The Spanish group has also shown that BTD is superior in CR rate to TD both pre- and post-transplant and also in PFS. With regard to lenalidomide, two large randomized studies have shown that the majority of

patients (>85%) respond to lenalidomide plus dexamethasone induction, but a minimum of four to six cycles would probably be required to achieve a substantial number of CRs. Thalidomide or bortezomib combinations did not affect stem cell collection or granulocyte and platelet recovery after transplantation. For lenalidomide, three recent reports indicate a decrease in CD34-positive cells collected and recommended harvesting early in the course of induction with lenalidomide and/or using cyclophosphamide along with G-CSF. It is evident that the pre-transplant induction regimen should be a triple combination based on bortezomib and dexamethasone. No data are available to draw conclusions regarding the superiority of one combination, such as BTD, BLD, BCD or BAD over the other.

### Autologous stem cell transplantation

High-dose therapy (usually melphalan 200 mg/m<sup>2</sup>) followed by autologous SCT prolonged OS compared with standard-dose therapy in prospective randomized trials conducted by the French (IFM) and English (MRC) groups and has provided evidence for more than 10-year survivorship in at least a subset of patients. Nevertheless, although the SWOG 9321 study in the USA, the French MAG91 study and the Spanish PETHEMA-94 trial confirmed the benefit of autologous SCT in terms of RR and event-free survival (EFS), they did not find superiority in terms of survival compared with standard-dose therapy. These discrepancies can be partly explained by differences in study design, differences in the conditioning regimens and, particularly, differences in the intensity and duration of the chemotherapy arm (the dose of alkylating agents and steroids was higher in the SWOG and Spanish trials, which may explain why OS for



conventionally treated patients was longer in these two studies compared with the IFM and MRC trials). Despite these discrepancies, high-dose therapy is currently considered the standard of care for younger patients with MM, mainly based on the benefit for RR and EFS.

In the setting of novel agents, it is also important to define whether autologous SCT enhances the RRs obtained with these new induction regimens. As mentioned above, studies based on bortezomib combinations, particularly those using BTd or PAD, have shown that the CR rate was improved following autologous SCT (Table 29.8), suggesting that induction with novel agents and autologous SCT are complementary rather than alternative treatment approaches. Nevertheless, the benefit in terms of EFS and OS remains to be seen. Data on lenalidomide are very encouraging, though still scanty. However, some investigators argue that this approach may be challenged by the optimal results obtained with 'long-term' treatment with novel combinations (i.e. lenalidomide plus dexamethasone).

With regard to tandem autologous SCT, its use will decrease since according to the French and Italian experience, only patients achieving less than a VGPR with the first transplant benefit from the second; nevertheless, recent data suggest that tandem transplant may be valuable in patients with high-risk cytogenetics. Second transplant at relapse may be increasingly used, providing that the duration of the response to the first transplant has lasted for more than 2–3 years.

### Consolidation and maintenance

The concept of consolidation with short-term therapy consisting of two or three full-dose cycles in order to further decrease the tumour mass is most promising and there are international trials investigating the role of consolidation after ASCT.

The next step in the sequence of treatment is maintenance. Interferon and/or corticosteroids have shown little benefit and have been abandoned. The availability of novel agents (particularly thalidomide and lenalidomide, which are available in oral formulations) has transformed the concept of maintenance in an attempt to prolong the duration of responses after transplantation. Six randomized trials have investigated the role of maintenance with thalidomide. In all six there was a benefit in PFS (6 months prolongation according to a meta-analysis),

but only in three was OS prolonged. This raises an important concern about whether the continuous use of novel agents may induce more resistant relapses with shorter survival after relapse in some studies. Two large randomized studies, by the IFM and the CALGB groups, of lenalidomide maintenance versus placebo have shown a significant benefit in PFS and in the CALGB trial also a significant prolongation of OS. However, there was an initial concern on the occurrence of second primary malignancies with lenalidomide in both trials and a short survival after relapse in the French study. A recent Italian trial also showed the benefit of lenalidomide maintenance. Regarding bortezomib maintenance, in two trials there was a benefit in PFS, but in OS only in one. Several prospective international trials on the role of maintenance are ongoing.

### Allogeneic stem cell transplantation

Allogeneic SCT remains the only curative therapeutic approach in MM. However, it is associated with a high TRM (up to 30–50%) and high morbidity, mainly due to chronic graft-versus-host disease (GVHD). Accordingly, it should be used in carefully defined situations and preferably within the context of clinical trials. In order to decrease TRM, different reduced-intensity conditioning regimens (allo-RIC), mainly based on fludarabine and melphalan or fludarabine plus radiotherapy (2 Gy) have been introduced. The TRM decreases to 15 to 25%, but this is associated with a higher incidence of relapses. In a prospective randomized trial, the French group compared double autologous SCT with autologous SCT followed by allo-RIC among patients displaying poor prognostic features (high  $\beta_2$ -microglobulin and monosomy 13). The results of double autologous SCT or autologous SCT followed by allo-RIC were similar. In contrast, the Italian group, using a similar approach, has described an improvement in terms of OS among patients receiving autologous SCT followed by allo-RIC compared with double autologous SCT. The Spanish group also reported a comparison between double autologous SCT and autologous SCT followed by allo-RIC in patients failing to achieve at least near CR after a first autologous SCT. Although there was a higher increase in CR rate and a trend towards a longer PFS in favour of allo-RIC, there was a statistical difference in EFS and OS. The EBMT has reported the updated results of allo-RIC versus ASCT

**Table 29.8** Result of randomized trials comparing autologous SCT with chemotherapy.

	Patients	CR (%)	EFS (months)	OS (months)
IFM90 (Attal <i>et al.</i> 1996)	200	22/5	28/18	57/44
MRC 03 (Child <i>et al.</i> 2003)	401	44/8	31/19	54/42
PETHEMA 95 (Bladé <i>et al.</i> 2005)	185	30/11	42/33	61/66
US-Intergroup (Barlogie <i>et al.</i> 2006)	516	11/11	25/21	58/53

CR, complete remission; EFS, event-free survival; OS, overall survival.



after a median follow-up of 7 years, showing a significant benefit in PFS and OS in favour of allo-RIC. Differences in patient characteristics, GVHD prophylaxis and conditioning regimens could contribute to these discrepant results. Moreover, unfortunately, a high proportion of patients developed extramedullary relapses without bone marrow involvement, indicating that although the disease may be under control in the bone marrow milieu, extramedullary spread may occur. In any event, about 10 to 15% of patients undergoing an allogeneic transplant are cured.

With regard to the use of allogeneic SCT as rescue therapy, a prerequisite is to obtain a CR or VGPR before the transplant, since most patients with active disease will not benefit from this procedure. Once again these transplants should be performed by experienced groups and within clinical trials. Donor lymphocyte infusions given for relapsed myeloma following allogeneic transplantation induce responses in 30–50% of patients, but unfortunately the long-term efficacy is limited.

### Treatment of newly diagnosed elderly and non-transplant candidate patients

Melphalan + prednisone (MP) has been the gold standard for over 40 years; however, the scenario has completely changed with the introduction of novel agents such as thalidomide or bortezomib, and lenalidomide.

Six randomized trials have compared thalidomide (T) + MP (MPT) versus MP, showing significantly higher RR in the MPT arm (59% versus 37%) (CR 10% versus 2.5%), as well as longer PFS/TTP (prolongation in PFS of 5.4 months). However, only in the three studies, MPT treatment was associated with a significant prolongation in OS (median of 6 months benefit). Based on these data MPT has been approved as a standard of care. The toxicity associated with the high dose of thalidomide, used in some of these trials, may contribute to explain the survival discrepancies. Data from the MRC myeloma IX trial shows that the combination of cyclophosphamide + thalidomide + dexamethasone (CTD) is superior to MP in terms of RR (82% versus 49%), but not in OS. MP has also been compared with thalidomide + dexamethasone (TD) and although the RR was higher in the experimental arm, the OS was shorter. It should be noted that in this last trial, TD treatment was associated with a higher rate of early discontinuations due to toxicity, and higher mortality, particularly during the first year.

Lenalidomide (Len) has also been combined with MP. A randomized trial comparing MP versus Len + MP, using Len either only as part of the induction or also as maintenance, showed a significantly longer PFS for the maintenance approach (31 versus 14 and 12 months, respectively), but no significant differences in OS. A large clinical trial, including 1600 patients, has compared Len-dex (low dose dexamethasone 40 mg weekly) until progression versus Len-dex fixed time (18 cycles) versus MPT (9 cycles). Initial results show a significant advantage for continuous Len-dex treatment, both in terms of PFS

(25.5 versus 20.7 versus 21.2 months, respectively) and OS (59.4%, 55.7% and 51.4% OS at 4 years,  $P = 0.01$ ). Based on these data continuous LEN-dex could become a new standard (without alkylator) for newly diagnosed non-transplant candidate patients.

The proteasome inhibitor bortezomib (B) has been tested in combination with MP in a pilot study conducted by the Spanish group; the positive results were confirmed in a large randomized study, which compared BMP versus MP (9 cycles in each arm). The RR for BMP versus MP were 71% versus 35%, with 30% versus 4% CR. BMP treatment was associated with a longer TTP (24 versus 16.6 months) and OS at 3 years of 72% versus 59%. The results were updated after more than 5 years follow-up and confirmed a prolongation of 13 months in OS for BMP. This combination has been approved as a standard of care by EMEA and FDA. In an attempt to optimize the treatment of elderly untreated MM patients with VMP, the Spanish and Italian Myeloma groups (GEM/PETHEMA and GIMEMA) activated two randomized trials, exploring bortezomib only once weekly instead of the standard twice weekly schedule. Results have indicated that the tolerability is increased substantially, and the efficacy is maintained with the reduced-dose bortezomib schedule (probably due to the better tolerability with fewer treatment discontinuations). Thus, grade 3/4 PN was only 5–7% with the reduced dose VMP regimen in the two studies. In line with this reduction in the frequency of PN, the rate of treatment discontinuations was low in both studies (8% and 10%). In addition, the French group has reported that when bortezomib is given by subcutaneous route of administration instead of the conventional intravenous route, the rate of grade 3/4 PN drops from 16% to 6%. New proteasome inhibitors such as carfilzomib or ixazomib (also called MLN9708, a twin brother of bortezomib in oral formulation) are being investigated in combination with either MP or Len-dex, with encouraging results. Bendamustine plus prednisone has been compared with MP and the former was associated with longer PFS (18 versus 11 months), but no longer OS.

Several trials have explored the value of maintenance treatment in the elderly population. Thalidomide was investigated in three studies and although some of them showed some benefit in PFS (ranging from 2 to 7 months), only one had benefit in OS and, accordingly, this approach has been abandoned. As mentioned above, continuous treatment with lenalidomide, both in the MPR and Len-dex trial have been associated with a significant prolongation in PFS (around 18 months benefit), which translated into longer OS in the second, but not in the first trial. As far as bortezomib maintenance is concerned, the Spanish group has investigated the value of 3 years of maintenance with either Btz-Thal or Btz-Pred (one pulse every three months) after a short course of 6 induction cycles with B-MP or B-Thal-P, and although this approach resulted in a long PFS of approximately 3 years, the overall benefit in OS remains to be seen. The Italian group has investigated the value of B-Thal

**Table 29.9** Results from randomized Phase III trials in newly diagnosed elderly patients.

Study	Induction regimen	N	Maintenance regimen	CR (%)	ORR(%)	PFS/TTP (months)	Median OS (months or %)
<b>Alkylator-based induction regimens</b>							
<i>Melphalan-based combinations</i>							
Palumbo 2006, 2008	MPT vs.	129	T until DP vs.	16	76	22	48
	MP	126	None	2.4	48	15	45
Facon 2007	MPT vs.	125	None	13	76	28	52
	MP	196	None	2	35	18	33
Hulin 2009	MPT vs.	113	None	7	62	24	44
	MP	116	None	1	31	19	29
Wijermans 2010	MPT vs.	165	T until DP vs.	N/A	66	13	40
	MP	167	None	N/A	45	9	31
Beksac 2011	MPT vs.	60	None vs.	58	9	21	28
	MP	62	None	38	9	14	26
Waage 2010	MPT vs.	182	T until DP vs.	13	57	15	29
	MP	181	None	4	40	14	32
Palumbo 2012	MPR-R	153	R until DP	18	77	31	70% at 3 years
	MPR	152	Placebo until DP	13	67	15	62% at 3 years
	MP	154	Placebo until DP	5	49	12	66% at 3 years
San Miguel 2013	MPV	344	None	30	71	N/A	56
	MP	338	None	4	35	N/A	43
Mateos 2012	VMP vs.	130	Randomized to VT	20	80	37	60% at 5 years
	VTP	130	or VP up to 3 years	28	81	32	53% at 5 years
Palumbo 2010	VMP vs.	257	None	24	81	27	51% at 5 years
	VMPT	254	VT up to 2 years	38	89	37	61% at 5 years
Nievizsky 2011	VMP	167	V (five cycles) in all arms	32	69	N/A	N/A
<i>Cyclophosphamide-based combinations</i>							
Morgan 2011	CTDa	426	Randomized to T or	13	64	13	33
	MP	423	not until DP	2	33	12	31
<i>Bendamustine-based combinations</i>							
Ponisch 2006	BP	68	None	32	75	18	32
	MP	63	None	13	70	11	33
<i>Non-alkylator-based induction regimens*</i>							
Ludwig 2009	TD	NS	Randomized to IFN	2	68	17	42
	MP	NS	or IFN-T	2	50	21	49
Nievizsky 2011	VD	168	V (five cycles) in all	24	73	NA	NA
	VTD	167	arms	36	80		
Rajkumar 2010	Len/Dex (RD)	214	None	5	81	19	75% at 2 years
	Len/dex (Rd)	208	None	4	70	25	87% at 2 years
Facon 2013	Len-dex (cont)	535	Continuous Len	15.1	75.1	25.5	59.4% at 4 years
	Len-dex (18 months)	541	None	14.2	73.4	20.7	55.7% at 4 years
	MPT	547	None	9.3	62.3	21.2	51.4% at 4 years

\*Also VTP (from the randomized trial MVP versus VTP (Mateos 2012)).

maintenance after induction with B-MPT, as compared with 9 cycles of Btz-MP; continuous treatment was associated with a longer PFS (37 versus 27 months), as well as a longer OS (67% versus 55% at 4 years).

A controversial issue is whether there is any preference for one of the novel combinations. An individualized treatment approach would probably be valuable: 1) for patients with previous history or risk of deep venous thrombosis, BMP could be the preferable option; 2) in patients with pre-existing peripheral neuropathy, Len-MP or better Len-dex (continuous) should be the choice; 3) in patients with renal insufficiency, BMP is the most safe approach, although Len-dex can also be used; 4) in patients living long distances from hospital, oral treatment (MPT or even better Len-dex) would be preferable; 5) in patients with poor compliance with treatment, BzMP could be better; 6) in fragile patients probably Len-dex is better tolerated, finally, 7) if cost is an issue MPT or Cyclo-TD are the cheapest options.

In patients >75 years or with frail condition it would be recommended to use modified regimens, with a lower dose of thalidomide (100 mg); or bortezomib (weekly schedule or 1 mg/m<sup>2</sup>). One additional possibility in these patients is to substitute melphalan by cyclophosphamide (50 mg/day or 1g/21days), since this latter agent is less myelotoxic. Lenalidomide do not require dose reduction if combined with only low dose dexamethasone, but 15 mg should be used if combined with MP. In very elderly patients, special attention must be paid to infectious episodes (require active treatment) and renal function (appropriate hydration), particularly during the first three months of treatment when they are responsible for the high incidence of early deaths. Ongoing studies will establish optimal dosing and treatment schedules for different populations with the aim of maximizing efficacy and improving tolerability.

## Treatment at relapse

It is important to separate the young (<65 years) from the elderly (>65 years) patients. In young patients relapsing after transplantation, we discriminate three cohorts of patients: early relapse (<1 year), intermediate relapse (1–3 years) and late relapse (>3 years). If the relapse occurs within the first year after transplantation, patients should be immediately considered high risk and, in order to overcome drug resistance, rescued with either a combination of all potentially effective drugs (e.g. BTD plus cisplatin, Adriamycin, cyclophosphamide and etoposide; or bortezomib, lenalidomide and dexamethasone) or alternating cycles of two combinations of non-cross-resistant agents (BCD alternating with lenalidomide/dexamethasone). If  $\geq$ PR is achieved, the patient could proceed to allogeneic SCT with RIC, although this must still be considered an investigational approach.

If relapse occurs 1–3 years after autologous SCT, we would favour rescue with novel agents used in a sequential (not simultaneous) manner, starting with one line of treatment (different from the one used as induction) and shifting to the second and

subsequent lines only when disease progression occurs. Within this category of patients, those under 60 years old with an HLA-identical donor and a suboptimal response to the first line of treatment should be considered for allogeneic SCT with RIC. Finally, if relapse occurs more than 3 years after the first autologous SCT, an attractive possibility is re-induction with the initial treatment or other novel-agent combination, followed by a second autologous SCT.

In elderly patients, treatment decisions at relapse must take into account the general condition of the patient. Once the patient relapses, after up-front treatment, the durations of subsequent responses to rescue therapies are progressively shortened. Therefore, the current goal in relapsed MM is to optimize the efficacy of novel drugs through their most appropriate combinations, to establish optimal sequences of treatment and to promote active clinical research on experimental agents that have already shown promising activity in *in vitro* and animal models.

At first relapse, a regimen based on novel drugs (lenalidomide or bortezomib) and different from that used as induction should be instituted. Table 29.10 summarizes the most relevant results and combinations reported in relapsed patients. Bortezomib as a single agent has been shown to be significantly superior to high-dose dexamethasone in relapsed/refractory patients (RR 43% versus 18%; CR 16% versus 1%; TTP 6 versus 3 months). The addition of pegylated doxorubicin increased EFS to 9.3 months. With regard to lenalidomide, a large randomized trial has shown that lenalidomide plus dexamethasone is significantly superior to dexamethasone alone (RR 60% versus 20%; CR 15% versus 2%; TTP 11.1 versus 4.7 months). The most widely used regimens at relapse include:

- lenalidomide/dexamethasone
- bortezomib/dexamethasone or bortezomib/liposomal doxorubicin with or without dexamethasone or bortezomib/cyclophosphamide/dexamethasone (Table 29.10).

At second or subsequent relapse, usually after the patient has already failed bortezomib and at least one immunomodulator, a clinical trial with experimental agents should be encouraged (see section on 'promising new drugs'). If the patient is not a candidate for active therapy, palliative treatment with oral cyclophosphamide (50 mg/day) and prednisone (30 mg on alternating days) can be considered.

## Side-effects associated with novel agents

Because of the previous history of thalidomide, a major concern was its toxicity profile. The side-effects are dose related and the most common include constipation, weakness, somnolence and neuropathy. Peripheral neuropathy is a common adverse event with thalidomide therapy and often limits the dose and duration of treatment. The use of combination therapy has raised concerns about an increased risk of DVT.

**Table 29.10** Relapse/refractory patients: response to thalidomide, lenalidomide and bortezomib; single agents and combinations.

Drug/combination	No. of patients	Response rate		Study
		PR or better (%)	CR (%)	
<i>Thalidomide-based combinations</i>				
T monotherapy (200–800 mg)	169	24	2	Singhal ( <i>N Engl J Med</i> 1999)
T monotherapy (meta-analysis)	1629	28	1.6	Glasmacher ( <i>Br J Haematol</i> 2005)
TD	>400	42–58	3–13	Several*
TD vs. placebo-D	116	65 vs. 28	NR	Fernand <i>et al.</i> (ASH 2006)
TCD	>200	56–76	5–20	Several†
<i>Lenalidomide-based combinations</i>				
L monotherapy	104	14	4	Richardson ( <i>Blood</i> 2006)
LD vs. D	175 vs. 176	60 vs. 22	15 vs. 2	Weber and Dimopoulos ( <i>N Engl J Med</i> 2007)
LAD	69	87	23	Knop (ASH 2007)
Pegylated liposomal doxorubicin + VDL	62	75	29 (CR + n-CR)	Baz ( <i>Ann Oncol</i> 2007)
LCD	21	65	NR	Morgan ( <i>Br J Haematol</i> 2007)
<i>Bortezomib-based combinations</i>				
B monotherapy vs. D	669	43 vs. 18	16 vs. 1	Richardson ( <i>N Engl J Med</i> 2005)
Pegylated liposomal doxorubicin + B vs. B monotherapy	646	48 vs. 43	14 vs. 11	Orlowski ( <i>J Clin Oncol</i> 2007)
BM	26	47	11	Berenson ( <i>J Clin Oncol</i> 2006)
BM	21	68	34 (CR + n-CR)	Popat (ASH 2007)
BCP	37	88	40	Reece ( <i>J Clin Oncol</i> 2008)
BCD	50	82	16	Kropff ( <i>Br J Haematol</i> 2007)
BCD	47	75	31	Davies ( <i>Haematologica</i> 2007)
<i>Immunomodulators (thalidomide/lenalidomide) plus bortezomib</i>				
BT ± D	85	55	16 (CR + n-CR)	Pineda-Román ( <i>Leukemia</i> 2008)
BT + pegylated liposomal doxorubicin	21	56	22 (CR + n-CR)	Chanan-Khan ( <i>Leukemia and Lymphoma</i> 2005)
BTAD	20	63	24 (CR + n-CR)	Hollmig (ASH 2006)
BTMP	30	67%	14 (CR), 7 (n-CR)	Palumbo ( <i>Blood</i> 2007)
BTMD	53	60	11	Terpos ( <i>Leukemia</i> 2008)
BL	27	79	33	Richardson (ASH 2007)

\*Weber (*J Clin Oncol* 2003), Dimopoulos (*Ann Oncol* 2001) and Palumbo (*Haematologica* 2001).

†Kropff (*Haematol J* 2003), García-Sanz (*Leukemia* 2004) and Dimopoulos (*Haematol J* 2004).

A: Adriamycin, B: bortezomib, C: cyclophosphamide, D: dexamethasone, L: lenalidomide, M: melphalan, P: prednisone, T: thalidomide, V: vincristine, CR: complete remission, n-CR: near complete remission, ASH: American Society of Hematology (Annual Meeting).

Apparently the major risk of DVT occurs when tumour load is high and thalidomide is combined with chemotherapy, especially Adriamycin. Accordingly, in this setting, anticoagulant prophylaxis with low-molecular-weight heparin (LMWH) or aspirin is mandatory. Current data suggest that lenalidomide is better tolerated than thalidomide in several aspects: it does not usually produce clinically significant somnolence, constipation or neuropathy, although the incidence of myelosuppression is higher, mainly neutropenia (grade 3 in 17–30%) and

thrombocytopenia, which are manageable with dose reduction and growth factor support. Similarly to thalidomide, lenalidomide is associated with a higher risk of DVT (5–25%) and the risk increases in patients with comorbidities, previous history of DVT, concomitant use of erythropoietin, high-dose dexamethasone, anthracyclines or high tumour mass. For these reasons, anticoagulant prophylaxis with LMWH or aspirin is mandatory. The most frequent toxicities of bortezomib include fatigue, gastrointestinal symptoms, cyclical thrombocytopenia and,

particularly, peripheral neuropathy. This latter side-effect, classified as grade 3 in 9–20% of patients, is the main reason for treatment discontinuation, and the early detection of peripheral neuropathy is most important in order to reduce the dose or frequency of injections. The use of a weekly schedule of bortezomib and particularly the subcutaneous administration has resulted in a significant decrease in peripheral neuropathy. Concerning panobinostat thrombocytopenic and gastrointestinal effects is the most relevant toxicity. Elotuzumab and daratumumab can produce infusion reactions.

### Promising new drugs

Undoubtedly, the development of proteasome inhibitors and immunomodulatory drugs (IMiDs) and the success of these agents in multiple myeloma has revolutionized the way we think about tumour biology and treatment of this disease. However, as mentioned previously, most patients eventually become resistant to these drugs, indicating that novel agents and combination strategies are clearly needed in the setting of relapsed and refractory disease.

The third-generation IMiD, pomalidomide, in combination with dexamethasone has demonstrated substantial efficacy in patients with pretreated multiple myeloma, including those refractory to lenalidomide or lenalidomide + bortezomib. In a cohort of patients with relapsed multiple myeloma in which 62% of patients had received prior IMiDs, pomalidomide + dexamethasone produced a response rate of 65% ( $\geq$ PR) and a PFS of 13 months. In patients with lenalidomide-refractory disease, approximately 25 to 35% responded to pomalidomide. This was confirmed in the Phase III randomized MM-003 trial, comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in patients who had failed prior bortezomib and lenalidomide. The combination significantly improved the primary endpoint of median PFS (4 versus 1.9 months, HR 0.50;  $P < .001$ ). In addition, a benefit in median OS was also observed for pomalidomide-dexamethasone compared to high-dose dexamethasone (13.1 versus 8.1 months, HR 0.72;  $P = 0.009$ ). This data suggests pomalidomide/dexamethasone may become a new standard for patients who are refractory to lenalidomide and bortezomib. Triple combinations of pomalidomide with cyclophosphamide-prednisone or with bortezomib-dexamethasone are being investigated and apparently duplicate the PFS.

The second-generation proteasome inhibitor, carfilzomib, has also shown encouraging efficacy in heavily pretreated MM patients. Thus, a response rate of 50% ( $\geq$ PR) with PFS of  $>8$  months is achieved when used as single agent, with 16% responses in Btz-refractory patients. In a Phase II trial, including lenalidomide refractory patients, carfilzomib in combination with Len-Dex showed 69%  $\geq$ PR with a PFS of 11.8 months. Of note, the incidence of PN is very low ( $<3\%$ ). Combinations with pomalidomide, cyclophosphamide or panobinostat

are also being tested. Moreover, three Phase III trials have been completed. The FOCUS trial has compared carfilzomib single agent with best supportive care in patients with very advanced disease showing similar outcome. The ENDEAVOR trial has compared carfilzomib + dexamethasone versus bortezomib + dexamethasone in relapsing patients; the first option achieved higher response rate (77% versus 63%) and longer PFS (18.7 versus 9.4 months). The ASPIRE study has investigated the addition of carfilzomib to the combination of lenalidomide and dexamethasone (CRd versus Rd). CRd was associated with longer PFS (26.3 versus 17.6 months) and OS (HR, 0.79). This CRd scheme has shown impressive preliminary results in newly diagnosed patients. Furthermore, a new oral proteasome inhibitor Ixazomib (MLN9708) is already in clinical trials. In relapse/refractory patients (most of them previously exposed to bortezomib)  $\geq$ PR was achieved in 15% of cases, with very low frequency of G3 PN. Based on these encouraging results Ixazomib is being studied in a Phase III trial in combination with Rd, not only in relapsed patients, but also in newly diagnosed patients in which this later combination has shown in a pilot study 92%  $\geq$ PR. Other oral proteasome inhibitors, such as oprozomib or marizomib are also at early phase of development.

Another drug currently under investigation in relapsed/refractory multiple myeloma is bendamustine, which is a hybrid between an alkylating agent and a purine analogue. As a single agent, it produced an ORR of 31% in patients with relapsed disease following high-dose therapy. Combinations of bendamustine with bortezomib, thalidomide or lenalidomide increase response rates substantially. Numerous ongoing clinical trials are investigating the role of bendamustine in patients with relapsed and/or refractory multiple myeloma.

Agents with novel mechanisms of action are also emerging, including monoclonal antibodies. The monoclonal antibody most advanced in clinical development for multiple myeloma is elotuzumab, a humanized IgG1 antibody targeting the CS1 glycoprotein. This cell surface glycoprotein is highly expressed in myeloma cells with little to no expression in normal tissues. The mechanism of action of elotuzumab is primarily through natural killer-cell-mediated ADCC. While elotuzumab monotherapy only elicited modest activity in patients with multiple myeloma, the addition of lenalidomide and low-dose dexamethasone resulted in an ORR of 82% in a Phase I trial of relapsed or refractory myeloma. The second type of monoclonal antibody under investigation is anti-CD38 (daratumumab, SAR650984). Results from phase I/II dose escalation studies have demonstrated activity in monotherapy, with 30 to 40% responses at the optimized doses, and only mild infusion reactions, which were well controlled with steroids. In the SIRIUS trial that included 112 heavily pre-treated and double refractory MM patients, daratumumab single agent induced 29% RR, with a DOR of 7.4 months and a PFS of 3.7 months. These positive results has prompted the investigation of anti-CD38 in combination with lenalidomide plus dexamethasone, with RR close to 90% in



lenalidomide sensitive patients and 50% in patients previously refractory to lenalidomide. Combinations with bortezomib are also under investigation.

The positive results of this combination in a phase II trial, with a PFS of 26.9 months, supported the activation of a large randomized trial (ELOQUENT) in relapsed/refractory patients after 1–3 prior lines of therapy comparing lenalidomide+dexamethasone plus/minus elotuzumab; the triplet combination was associated with longer PFS (19.4 versus 14.9 months) but not differences in OS have been so far observed.

Deacetylase (DAC) inhibitors also have a novel mechanism of action in multiple myeloma. DAC enzymes remove the acetyl group from client proteins, including histones, p53, HIF-1 $\alpha$  and Hsp90. Single-agent DAC inhibitors have demonstrated only modest activity and minor responses or disease stabilization in multiple myeloma. However, there is a clear rationale for the combination of DAC inhibitors with proteasome inhibitors. Two unique mechanisms exist to remove unfolded or misfolded proteins within a cell; the ubiquitin-proteasome cascade that degrades ubiquitinated proteins and the aggresome. Aggresomal degradation can be inhibited by histone deacetylase 6 (HDAC 6) inhibitors, as HDAC 6 binds ubiquitinated protein complexes and microtubule complexes, shuttling proteins into the aggresome for degradation. In preclinical studies, simultaneous targeting of proteasome activity and aggresome activity triggered substantial accumulation of misfolded proteins and synergistic multiple myeloma cytotoxicity. Additional *in vitro* and *in vivo* studies showed that the pan-DAC inhibitor panobinostat was highly synergistic with bortezomib-dexamethasone in multiple myeloma cell lines and murine models.

This led to the VANTAGE 088 trial investigating bortezomib in combination with the broad-acting HDAC inhibitor vorinostat or placebo in relapsed multiple myeloma. Although the combination significantly improved ORR (54% versus 41%;  $P < 0.0001$ ), the PFS advantage was only 24 days compared to placebo (7.63 versus 6.83 months). The reasons for this are unclear and could be related to the adverse event profile or the omission of corticosteroids, which may play a role in the synergy of these combinations. In the Phase II PANORAMA 2 trial, the combination of panobinostat with bortezomib-dexamethasone produced a partial response in 35% of patients with relapsed and bortezomib-refractory multiple myeloma. An encouraging PFS of 4.9 months was also observed. The Phase III PANORAMA 1 trial of bortezomib/dexamethasone with or without panobinostat in relapsed/refractory multiple myeloma has recently been completed and the results show a superiority for PFS in the experimental arm. (PFS, 12 versus 8 months). The improvement in the outcomes appeared to be particularly of interest among patients who had been previously exposed to proteasome inhibitors and IMiDs (PFS, 12.5 versus 4.7 months).

Novel agents are also targeting signalling pathways important for multiple myeloma pathogenesis. One of the most important

signalling pathways for tumour cell survival and proliferation is the PI3K/mTOR pathway. Several agents have been developed to target these pathways, including the Akt inhibitor perifosine and the mTOR inhibitors everolimus and temsirolimus. These agents have demonstrated modest efficacy as single agents and are being evaluated in combination with proteasome inhibitors and IMiDs (Table 29.3). It may be advantageous to consider simultaneous inhibition of more than one molecule along the PI3K/mTOR pathway, as targeting only the TORC1 complex with a rapamycin analogue can lead to compensatory upregulation of PI3K and TORC2 activation.

The RAS/MEK/ERK pathway is also important in multiple myeloma for tumour growth and differentiation. In an *in vivo* mouse model evaluating IMiD activity and resistance, decreased ERK activation was observed when IMiDs were administered. In contrast, activation of ERK and MEK signalling occurred when tumours became resistant to IMiD therapy. The addition of a MEK inhibitor potentiated the activity of lenalidomide-dexamethasone and pomalidomide-dexamethasone in multiple myeloma cell lines, suggesting a rationale for combining ERK pathway inhibitors with IMiDs.

The kinase spindle protein inhibitor ARRY-520 is currently under investigation and demonstrating preliminary efficacy in multiple myeloma. Kinase spindle protein is required for multiple myeloma cell-cycle progression, and inhibition with ARRY-520 induces mitotic arrest and subsequent apoptosis. Phase II trial data demonstrated activity for this novel agent, including a  $\geq$ PR rate of 22% when ARRY-250 was combined with low-dose dexamethasone in patients refractory to bortezomib, lenalidomide and dexamethasone.

Selinexor, and oral selective inhibitor of Nuclear Export, that inhibit XPO 1 and as consequence activate tumour suppressor proteins and reduces oncoproteins is another promising drug. Finally, active research on immunotherapy, particularly targeting check point inhibitors (PD1, PDL1 ...) is underway.

The evolution of therapy for multiple myeloma is far from over, with continued discovery of new drugs and progress in our understanding of myeloma cell biology and prognostic factors. The future success of multiple myeloma treatment depends on the use of rationally designed drug combinations. Myeloma needs to be approached as a heterogeneous disease with distinct disease subtypes. This will allow individualization of therapy with newer agents and potentially make multiple myeloma a chronic disease.

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