Multiple myeloma

Shaji K. Kumar[1], Vincent Rajkumar[1], Robert A. Kyle[1], Mark van Duin[2], Pieter Sonneveld[2], María-Victoria Mateos[3], Francesca Gay[4] and Kenneth C. Anderson[5]

Abstract | Multiple myeloma is a malignancy of terminally differentiated plasma cells, and patients typically present with bone marrow infiltration of clonal plasma cells and monoclonal protein in the serum and/or urine. The diagnosis of multiple myeloma is made when clear end-organ damage attributable to the plasma cell proliferative disorder or when findings that suggest a high likelihood of their development are present. Distinguishing symptomatic multiple myeloma that requires treatment from the precursor stages of monoclonal gammopathy of undetermined significance and smouldering multiple myeloma is important, as observation is the standard for those conditions. Much progress has been made over the past decade in the understanding of disease biology and individualized treatment approaches. Several new classes of drugs, such as proteasome inhibitors and immunomodulatory drugs, have joined the traditional armamentarium (corticosteroids, alkylating agents and anthracyclines) and, along with high-dose therapy and autologous haemopoietic stem cell transplantation, have led to deeper and durable clinical responses. Indeed, an increasing proportion of patients are achieving lasting remissions, raising the possibility of cure for this disease. Success will probably depend on using combinations of effective agents and treating patients in the early stages of disease, such as patients with smouldering multiple myeloma.

Multiple myeloma is a malignancy of terminally differentiated plasma cells, and is the second most common haematological malignancy after non-Hodgkin lymphoma[1]. The malignant plasma cells are primarily resident in the bone marrow, but they can also be seen in the peripheral blood and other extramedullary sites, such as soft tissue and organs, especially late in the disease course[2]. In most patients, multiple myeloma is characterized by the secretion of a monoclonal immunoglobulin protein (also known as M protein or monoclonal protein), which is produced by the abnormal plasma cells. However, in 15–20% of patients, the multiple myeloma cells secrete only monoclonal free light chains, and, in <3% of patients, these cells secrete no monoclonal protein[3,4]. The clinical manifestations of disease are driven by monoclonal protein, the malignant cells or cytokines secreted by the malignant cells, and include signs of end-organ damage, such as hypercalcaemia, renal insufficiency, anaemia, and/or bone disease with lytic lesions (that is, lesions caused by a disease process) or pathological fractures, which are collectively known as CRAB features[5].

Multiple myeloma is part of a range of disorders referred to as the monoclonal gammopathies. Within these disorders, the most common is monoclonal gammopathy of undetermined significance (MGUS), which is characterized by the infiltration of clonal plasma cells into the bone marrow and the secretion of monoclonal protein. MGUS is asymptomatic and consistently precedes the development of multiple myeloma, with or without an identified intervening stage, referred to as smouldering multiple myeloma (SMM)[6–9] (FIG. 1). Nearly 15% of patients with MGUS will progress to multiple myeloma, and ~20% will progress to multiple myeloma or a related condition (such as AL amyloidosis, Waldenstrom macroglobulinaemia or a lymphoproliferative disorder) over 25 years.

Historically, the treatment of multiple myeloma has been triggered by the development of CRAB features. With increasing recognition of biomarkers that can identify patients at very high risk of progression to active disease (that is, multiple myeloma that requires treatment), the diagnostic criteria for monoclonal gammopathies have undergone revisions and allow some patients to commence treatment earlier. The past decade has seen a phenomenal change in our understanding of the monoclonal gammopathies, including an improved understanding of the underlying disease biology and the introduction of more-effective therapies and combinations of therapies. The use of genomic techniques has led to a better appreciation of the underlying genetic abnormalities of multiple myeloma, both at a chromosomal level and at a single gene level, pointing towards multiple myeloma not being a single disease, but a collection of diseases with a common clinical phenotype.

Correspondence to S.K.K.
Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, Minnesota 55905, USA.
kumar.shaji@mayo.edu

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Author addresses

[1]Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, Minnesota 55905, USA.
[2]Department of Haematology, Erasmus Medical Center, Rotterdam, The Netherlands.
[3]Department of Hematology, Hospital Universitario de Salamanca/IBSAL, Salamanca, Spain.
[4]Myeloma Unit, Division of Hematology, AOU CIttà della Salute e della Scienza di Torino, Turin, Italy.
[5]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA.

In this Primer, we provide a broad overview of the current understanding of multiple myeloma, including the epidemiology, pathogenesis, current approaches for the prevention of disease progression, various treatment options and the overall impact on aspects of quality of life (QOL), and, finally, the outlook for the future.

Epidemiology

Multiple myeloma has been estimated to account for 1.7% of all malignancies and 10% of all haematological malignancies in the United States in 2017 (REF. 1). Globally, the incidence varies and is highest in more-developed countries, such as the United States, western Europe and Australia (FIG. 2). The higher incidence in developed countries is probably owing to the availability of better diagnostic techniques, as well as a greater clinical awareness of the disease. The incidence of multiple myeloma is 2–3-times higher in black individuals than in white individuals[10], but is lower in Asian and Hispanic individuals[11].

In Olmsted County, Minnesota, USA, the average annual incidence of multiple myeloma has increased from ~1 case per 100,000 person-years between 1935 and 1944 to 2.9 cases per 100,000 person-years between 1945 and 1964 (REF. 12). Between 1945 and 2001, the age-adjusted incidence (adjusted with respect to the 2000 US population) was 4.6 per 100,000 person-years; however, no significant increase was observed over 3 year periods during this timeframe ($P=0.86$)[13]. The incidence of multiple myeloma in Malmo, Sweden, also remained stable between 1950 and 2005 (REF. 6). The major factor responsible for the non-significant trend suggesting an increase in incidence in multiple myeloma in many studies is improved case ascertainment, especially among elderly individuals. In the United States, mortality rates increased until the 1990s but decreased following the introduction of novel therapeutic agents in 2000 (REF. 14).

The prevalence of multiple myeloma has increased because of better diagnostic techniques and improved patient survival, owing to widespread use of autologous haematopoietic stem cell transplantation (ASCT) and the development of novel therapeutic agents[15].

Aetiology

Environmental and occupational exposures. The cause of multiple myeloma is unknown, although several studies have evaluated potential risk factors for this disease. In one study, the incidence of multiple myeloma was increased threefold among individuals who received radiation exposure of ≥0.5 Gy compared with control individuals, ≥20 years after exposure to the atomic bombs in Hiroshima and Nagasaki[16]. By contrast, a more recent analysis of the data from 1950 to 1987 with 2,778,000 person-years follow-up, suggested that individuals with a radiation exposure of <4 Gy did not have a significantly increased risk of multiple myeloma, compared with the remaining individuals[17]. Indeed, the investigators concluded that an increased risk of multiple myeloma following exposure to the atomic bombs has little supporting evidence[17].

Occupational exposures have been studied in many populations. A large meta-analysis of data from farmers in the central United States reported a relative risk of 1.38, but whether this increased risk was related to exposure to pesticides, solvents, infectious agents or other factors could not be determined[18]. In addition, male farmers in Iowa have an increased proportionate mortality ratio for multiple myeloma of 1.27 (REF. 19).

Exposure to hair dyes has been associated with an increased risk of multiple myeloma[20]. In addition, exposure to benzene and petroleum products has also been associated, but little evidence is available to support a causal relationship with the development of multiple myeloma[21].

Genetic factors. Eight families with two or more first-degree relatives with multiple myeloma have been reported[22]. In addition, the risk of MGUS in first-degree relatives of patients with multiple myeloma is increased by twofold[23].

Genome-wide association studies (GWAS) have identified multiple genetic loci associated with an increased risk of multiple myeloma, in addition to loci associated with an increased mortality in diagnosed patients. In one of the largest GWAS to date, eight new loci associated with risk of multiple myeloma were identified[24]. Several single-nucleotide polymorphisms (SNPs) that could lead to *MYC* activation (which is associated with multiple myeloma progression) were also identified. Other GWAS have identified loci associated with an inferior survival (such as 6p25 and 16p13) in patients[25,26]. In addition, some SNPs have been associated with clinical presentation or the development of drug-related toxicity, such as bortezomib-induced neuropathy[27,28].

Mechanisms/pathophysiology

Insight into B cell development and plasma cell biology is essential for understanding multiple myeloma. Plasma cells develop from haematopoietic stem cells, which undergo several rounds of differentiation in the bone marrow and secondary lymphoid organs to B cells and eventually to plasma cells. In the bone marrow, immature B cells undergo V(D)J rearrangement, a process that generates their diverse primary immunoglobulin repertoire[29]. B cells with a IgH–IgL complex (that is, a B cell receptor) on the cell surface migrate to secondary lymphoid organs, such as the lymph node or the spleen. In these secondary lymphoid organs, the B cells undergo several processes (such as affinity maturation, somatic hypermutation and class-switch recombination) that result in the production of antibodies that have a high affinity for specific antigens and with different functional properties (that is,

different immunoglobulins). Double-strand DNA breaks in the immunoglobulin loci are required for class-switch recombination and somatic hypermutation. However, these DNA breaks can fuse with other breaks that occur elsewhere in the genome, leading to aberrant fusions of DNA and chromosomal translocations. Most of these chromosomal translocations are inconsequential, as these cells do not produce progeny, which is most likely as a result of a lack of growth advantage conferred by the translocation. However, translocations that involve specific oncogenes can give cells a growth advantage, which could lead to the development of pathological states, such as MGUS, SMM and eventually multiple myeloma. Thus, chromosomal translocations are a possible initiating event for a subset of multiple myeloma cases. An alternative, and possibly cooperating, putative initiating event is aneuploidy, with hyperdiploidy as the most frequent entity, as outlined below. Models of multiple myeloma development, including the use of animal models and cell lines (BOX 1), have contributed to our understanding of this disease.

Genetic alterations

Multiple myeloma is clinically and biologically heterogeneous with several genetic alterations proposed as driving events in myelomagenesis[30,31]. As previously discussed, primary genetic events associated with the development of the precursor states, and possibly the development of multiple myeloma, are chromosomal translocations and aneuploidy. Although there is no specific genetic event that marks the transition from MGUS and SMM to multiple myeloma, patients with certain genetic and epigenetic aberrations, including DNA methylation and microRNA (miRNA) expression, have a higher chance of progressing to multiple myeloma.

Chromosomal defects. Translocations that involve *IGH* (that is, genes encoding the immunoglobulin heavy chains) and a limited set of recurrent partner genes, such as *NSD2* (also known as *MMSET*), *FGFR3* (encoding fibroblast growth factor receptor 3) and *CCND1* (encoding cyclin D1), represent an important class of primary events identified in MGUS, SMM and multiple myeloma[30–33]. Indeed, fusion of the *IGH* enhancer to other genes results in the enhanced expression of the partner genes. The underlying mechanism of translocations is mostly abnormal class-switch recombination during plasma cell development, but other mechanisms, such as abnormal V(D)J rearrangement has also been implicated in a subset of cases[34]. The occurrence of site-specific DNA damage has been reported to explain which genes are recurrently fused to *IGH*[35]. Translocation t(11;14), which is found in 14% of all patients with multiple myeloma, results in increased expression of *CCND1*, whose product, cyclin D1, is important for cell cycle progression.

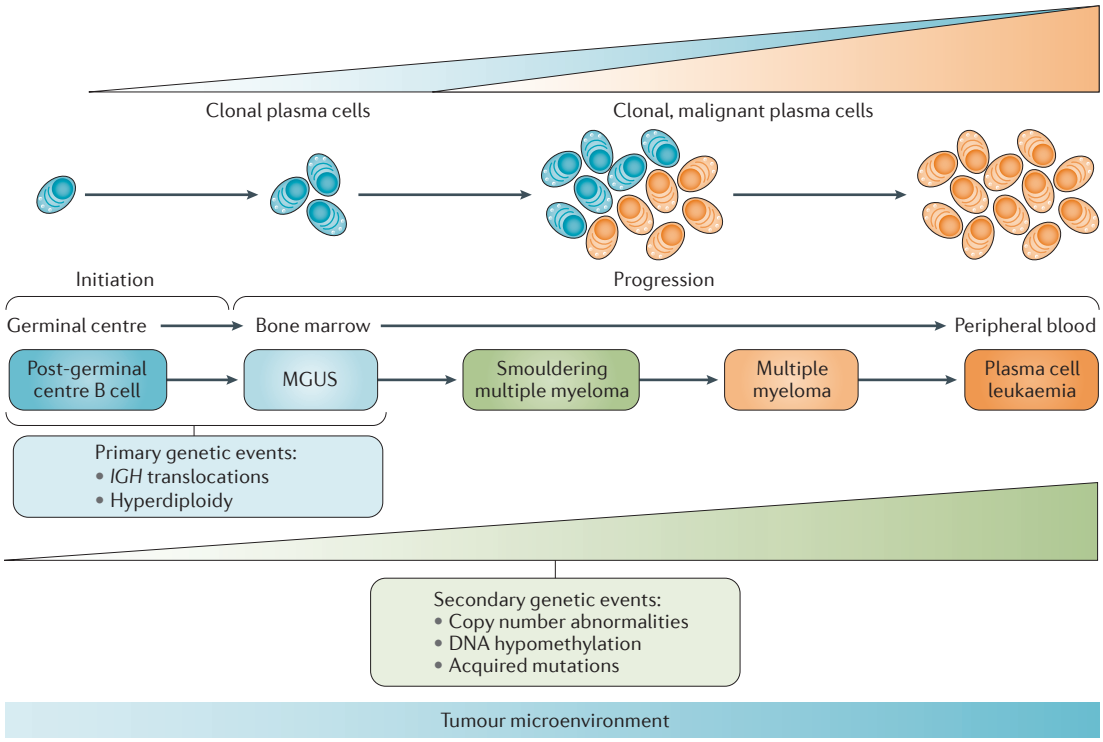

Figure 1 | **The development of monoclonal gammopathies.** The development of multiple myeloma is a multistep process, which starts with precursor disease states, such as monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM). Although MGUS, SMM and multiple myeloma are clinically well defined, many biological similarities between these disease states have been found. Multiple myeloma can progress to bone marrow-independent diseases, such as extramedullary myeloma and plasma cell leukaemia. Primary genetic events in the development of MGUS, SMM and multiple myeloma include chromosomal translocations involving the immunoglobulin heavy-chain genes (*IGH*) and aneuploidy (with hyperdiploidy as the most frequent entity). The number of secondary genetic alterations increases from MGUS to SMM and then to multiple myeloma.

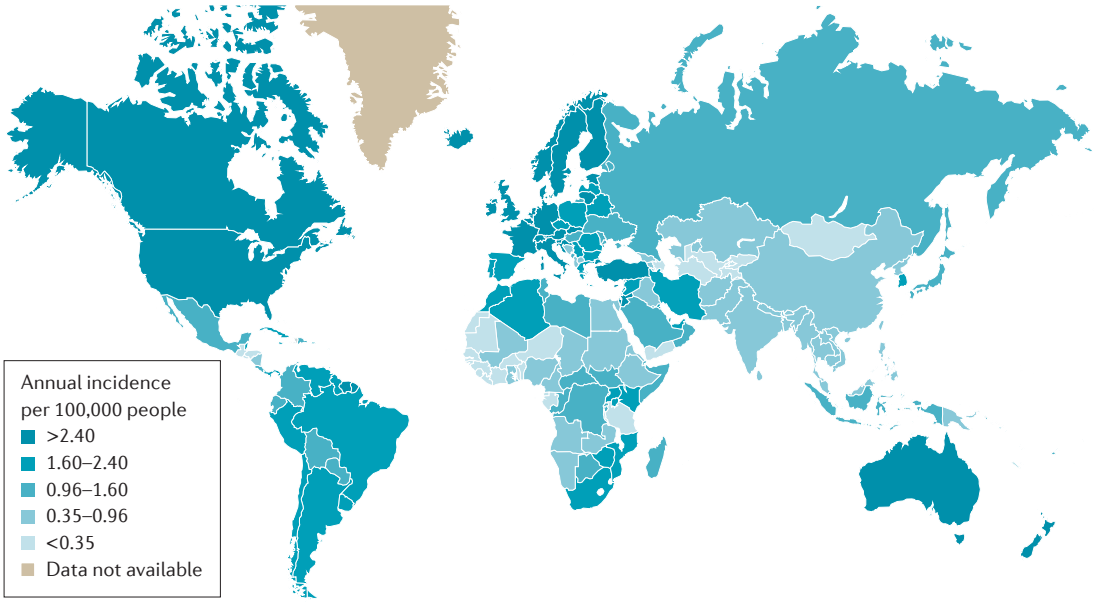

Figure 2 | **Incidence of multiple myeloma in 2012.** The incidence of multiple myeloma varies depending on the country, but is generally higher in more-developed countries, such as those in northern America and western Europe. Reproduced with permission from Ferlay J., Soerjomataram I., Ervik M., Dikshit R., Eser S., Mathers C., Rebelo M., Parkin D. M., Forman D., Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed June 19, 2017.

Translocation t(4;14) is found in 11% of patients with multiple myeloma and leads to overexpression of *NSD2* (which results in epigenetic dysregulation) and often *FGFR3*. Other recurrent translocations that involve *IGH* include t(14;16) (which involves *MAF*; found in 3% of patients), t(14;20) (involving *MAFB*; found in 1.5% of patients) and t(6;14) (involving *CCND3*; found in <1% of patients).

In two independent cross-sectional studies, the frequency of t(4;14) was 1–3% of patients with MGUS and 11–12% of patients with multiple myeloma[30–33], whereas the frequency of t(11;14) was found in 13% of patients with MGUS and 16% of those with multiple myeloma[36,37]. The median time to progression from SMM to multiple myeloma is shorter in patients with t(4;14) (28 months) than in patients with t(11;14) (55 months)[38], suggesting that t(4;14) cases might be more prone to undergo a secondary event required for progression.

Hyperdiploidy is the most frequent form of aneuploidy in multiple myeloma. Patients with hyperdiploidy are less likely to have a primary *IGH* translocation, but a small number of patients with an *IGH* translocation and hyperdiploidy have been identified. In a recent series of 965 patients with multiple myeloma characterized by SNP array, 35% of patients had <46 chromosomes (that is, they had hypodiploidy), 13% of patients had 46 chromosomes (that is, pseudodiploidy), 14% of patients had 47–50 chromosomes (that is, mild hyperdiploidy) and 38% of patients had >50 chromosomes (that is, large hyperdiploidy)[39]. Hyperdiploidy is characterized by co-occurring trisomies of some of all of chromosomes 3, 5, 7, 9, 11, 15 and 19 in patients with multiple myeloma. Despite the frequent co-occurrence of these trisomies, trisomies 3 and 5 have been reported to be associated with a good prognosis, whereas trisomy 21 is associated with worse outcome. Indeed, the poor prognosis conferred by t(4;14) seems to be cancelled out by co-occurrence of trisomies 3 and 5. In terms of ploidy, patients with hypodiploidy have the worst outlook, followed by patients with pseudodiploidy and hyperdiploidy. An interesting but rare subset of hypodiploidy is hyperhaploidy, in which patients have 30–33 chromosomes, with monosomies of most even numbered chromosomes and chromosomes 1, 13 and 13, and disomies of most odd numbered chromosomes, and chromosome 18; hyperdiploidy and hyperhaploidy might be the consequence of a defect in spindle apparatus and centrosome function[39–41] (see below).

Other chromosomal defects observed in patients with multiple myeloma include loss of the short arm of chromosome 1 (del(1p)), gain of the long arm of chromosome 1 (gain(1q)), deletion of the long arm of chromosome 13 (del(13q)) and loss of the short arm of chromosome 17 (del(17p))[30,31,42]. Increased occurrence of del(17p) and translocation t(8;14), linking the *IGH* enhancer on chromosome 14 with the *MYC* oncogene, is clearly associated with progression from newly diagnosed multiple myeloma to refractory disease and plasma cell leukaemia. MYC, an important regulator, was recently identified as a deregulated factor in up to 49% of patients with multiple myeloma, which included both newly diagnosed and previously treated patients. MYC regulates up to 15% of all genes, including upregulation of *CCND2*, which is involved in cell cycle regulation, and upregulation of *ENO1*, which is involved in glycolysis[43,44]. On the basis of gene expression profiling studies, several subgroups of multiple myeloma have been identified, which further reflects the genetic heterogeneity of these cells (BOX 2).

Secondary mutations and clonal evolution. Next-generation sequencing has shown a lack of a universal driver mutation in multiple myeloma, and the presence of coexistent subclones of malignant plasma cells with partially overlapping, unique mutations[30,34,45,46]. The most frequently occurring mutations in patients with multiple myeloma are in *KRAS* (in 23% of patients), *NRAS* (20%), *FAM46C* (11%), *DIS3* (11%) and *TP53* (8%). Other less frequently but recurrently mutated genes include *BRAF*, *TRAF3*, *PRDM1*, *CYLD*, *RB1*, *IRF4*, *EGR1*, *MAX*, *HIST1H1E* and *ACTG1* (REFS 34,45,46). These mutations can affect several cellular signalling pathways (FIG. 3). Preliminary RNA sequencing showed that the majority of mutated genes have low expression, suggesting that mRNA levels of these genes could be informative in the evaluation of mutation status[47].

The comparison of multiple myeloma cases at diagnosis and after treatment supports the concept of branching clonal development in a subset of patients. In patients with branching clonal development, one or more subclones appear, whereas others have disappeared. Other proposed patterns of clonal evolution include no change, subclonal shift and linear evolution, although the technical ability to detect subclones is naturally important in this classification. In the patients without change, the subclonal composition found at diagnosis is the same at relapse, suggesting that different subclones have responded similarly to the treatment. In patients with a subclonal shift, the subclones at diagnosis are also present at relapse, but the frequency of the subclones has changed and one clone has become more dominant than another. In patients with a linear pattern, a new subclone has emerged between diagnosis and relapse, which was absent at diagnosis[45,48]. The presence of subclonal mutations in multiple myeloma has consequences for treatments that target the mutated protein; for example, *BRAF* mutations have targeted therapies but occur in 6% of patients with multiple myeloma and often in <30% of multiple myeloma cells within these patients[46]. Although there are multiple targetable mutations, a strategy whereby multiple targeted therapies might be capable of the destruction of all malignant subclones is hard to envisage. Different biopsy sites within the same patient revealed partially overlapping mutations, in addition to different mutations, indicating a further level of genetic complexity. Whether this finding has implications for diagnostic procedures is currently not clear[49].

Although multiple myeloma is characterized by many mutations occurring in small subsets of patients, alterations in several cellular pathways can be distinguished, for example, the nuclear factor-κB (NF-κB) pathway[50,51]. Indeed, genetic abnormalities in 20% of patients result mostly in activation of the non-canonical NF-κB pathway, which can increase the expression of several anti-apoptotic proteins[52] (FIG. 3).

Epigenetic alterations. Epigenetic defects studied in multiple myeloma include altered DNA methylation, chromatin structure and miRNA deregulation. Median global methylation was shown to be variable in multiple myeloma, with some patients showing a global hypomethylation and others showing a global hypermethylation, compared with normal plasma cells. Levels of hypermethylation are similar in MGUS and multiple myeloma, whereas levels of hypomethylation are increased in multiple myeloma, suggesting that this might play a part in disease development[53,54]. DNA hypermethylation at enhancer regions, rather than promoters, was linked to reduced expression of genes associated with these enhancers[52]. In this context, the chromatin regulator bromodomain-containing protein 4 (BRD4) has been shown to bind at high levels to enhancer sites associated with genes that have a strong link to multiple myeloma, which include *MYC*, *IRF4* (which encodes interferon regulatory factor 4) and *CCND1* (REF. 55).

Several miRNAs are present at different levels in multiple myeloma cells, when compared to normal plasma cells, or MGUS cells, including upregulation of miR-19a and miR-19b in multiple myeloma[56]. miR-19a and miR-19b can contribute to Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway activation through targeting the JAK–STAT inhibitor suppressor of cytokine signalling 1 (SOCS1). JAK–STAT signalling is important in multiple myeloma for regulating sensitivity to cytokines, and consequentially survival[56–58]. In addition, reduced levels of miR-30-5p could be associated with increased levels of B cell CLL/lymphoma 9 protein (BCL9; a transcriptional co-activator of WNT–β-catenin signalling)[59]. Among the many targets of WNT–β-catenin signalling is MYC, which could result in increased cell survival[60].

Microenvironment

The interplay between multiple myeloma cells and the bone marrow microenvironment is crucial for myeloma development, treatment and progression (FIG. 4). Several cell types are found in the microenvironment, including haematopoietic cells (including B cells, T cells, natural killer cells, myeloid-derived suppressor cells and osteoclasts (which have a role in bone resorption)) and non-haematopoietic cells (including bone marrow stromal cells, osteoblasts (which have a role in bone formation) and endothelial cells). Collectively, these cells secrete several factors that can contribute to the migration and proliferation of multiple myeloma cells, and can also contribute to bone damage.

Box 1 | **Model systems**

Model systems used for the study of multiple myeloma include cell lines, mouse models and zebrafish models. The inherent difficulty of studying multiple myeloma is the inability to culture primary myeloma cells efficiently. Animal models include mice that spontaneously develop disease (the 5TMM model[145]), transgenic mice and xenografts. Xenografts allow for the study of primary multiple myeloma cells and include models that use human or rabbit bone microenvironments in the mouse, in which multiple myeloma cells can grow, and bone disease and response to drugs can be studied. In these models, artificial bone microenvironments can be used instead of those derived from a human or a rabbit[145,146]. Interestingly, transgenic mice, for example, the Vk*MYC model, in which *MYC* is under the control of Igκ light-chain regulatory elements, develop plasma cell tumours that represent human disease[145,147]. Recently, zebrafish were used to study dissemination and migration of human multiple myeloma cells; this model may have advantages over other model systems, in terms of ease of use: both cost and developmental time are reduced, and zebrafish are transparent, which enhances imaging[148].

Box 2 | **Genetic subgroups of multiple myeloma**

On the basis of clustering analysis, up to 10 subgroups of multiple myeloma have been described, which are characterized by distinct gene expression patterns. Some subgroups, such as the MF, MS and HY groups, overlap with and reflect frequent cytogenetic aberrations seen in patients with multiple myeloma, such as t(14;16) or t(14;20) (with overexpression of *MAF* and *MAFB*), t(4;14) (with overexpression of *NSD2* (also known as *MMSET*) and often *FGFR3*) and hyperdiploidy (with *TNFSF10* overexpressed in this group), respectively. Other subgroups demonstrate differential expression of other gene sets, such as overexpression of proliferation-related genes, overexpression of cancer testis antigens or overexpression of nuclear factor-κB pathway genes[149,150]. The subgroups MS and MF are associated with poor prognosis (as patients in these groups typically have t(4;14) and t(14;16)/t(14;20)). The subgroup PR is also associated with poor prognosis, as these patients might have overexpression of proliferation genes such as *TOP2A*, which may confer resistance to specific therapies. Purpose built classifiers based on gene expression profiling have proved to be much stronger indicators of high-risk multiple myeloma[151,152].

The migration of multiple myeloma cells to the bone marrow is similar to the homing of mature plasma cells and involves increased expression of CXC-chemokine receptor type 4 (CXCR4) on the cells, causing migration towards the stromal cell-derived factor 1 (SDF1; also known as CXCL12)-containing regions of the bone marrow niche[61]. Endothelial cells might have a role in multiple myeloma cell migration; endothelial cells secrete extracellular cyclophilin A (also known as peptidyl-prolyl cis–trans isomerase A), which binds to CD147 (also known as basigin (BSG)) on the surface of multiple myeloma cells, contributing to migration[62]. The formation of the initial clone in the bone marrow has been described as micrometastatic, and the formation of additional localization of multiple myeloma cells in the bone marrow as colonization[63].

As indicated below, interaction with bone marrow stromal cells alters the levels of factors involved in aberrant bone formation, including receptor activator of nuclear factor-κB ligand (RANKL; also known as TNFSF11) and osteoprotegerin (also known as TNFRSF11B)[31]. Extensive bone disease in patients with multiple myeloma is caused by increased activity and increased number of osteoclasts and reduced activity and number of osteoblasts[64]. Indeed, the interaction of multiple myeloma cells with bone marrow stromal cells and osteoblasts causes increased production of RANKL and reduced levels of osteoprotegerin[64]. RANKL binds to RANK (receptor activator of NF-κB; also known as TNFRSF11A), which is expressed by preosteoclasts, resulting in increased differentiation to osteoclasts. Osteoprotegerin is a decoy RANK receptor; as a consequence of reduced levels of this factor, effective RANKL levels are higher[65]. An imbalance in the number and activity of osteoclasts and osteoblasts results in the destruction of bone and the development of bone disease.

The importance of the microenvironment was further demonstrated by the report that binding of multiple myeloma cells to bone marrow stromal cells causes resistance to certain therapies, in a process termed cell adhesion-mediated drug resistance (CAMDR)[66]. High-throughput screens have identified drugs that have decreased efficacy in the presence of stroma, which also confirmed the original finding of CAMDR[67]. In the interplay between the microenvironment and multiple myeloma cells, exosomes might have a role[68]. In patients, exosomes from bone marrow stromal cells have lower content of some miRNAs (such as miR-15a) than exosomes from healthy individuals[68]; this might affect tumour growth and development as miR-15a is considered a tumour suppressor miRNA, with *BCL2*, *CCND1* and *CCND2*, among others, as proposed targets[69,70].

Factors produced in the microenvironment can be associated with angiogenesis. Indeed, vascular endothelial growth factor A (VEGFA), which is produced by bone marrow stromal cells, is a strong angiogenic factor, resulting in increased oxygen supply through increased, local abundance of blood vessels. Clinically, a high microvessel density indicative of increased angiogenesis was linked to a worse outcome[71].

Other mechanisms

Two important classes of drugs for the treatment of multiple myeloma are immunomodulatory drugs and proteasome inhibitors. Increased insight into the biology of multiple myeloma has been acquired through characterizing the in depth mechanism of specific treatments. For example, thalidomide, lenalidomide and pomalidomide target cereblon, which is part of an E3 ubiquitin ligase complex that causes ubiquitylation and subsequent degradation of several transcription factors (the DNA-binding protein Ikaros, the zinc finger protein Aiolos and casein kinase I isoform-α (CK1a)). Expression of Ikaros and Aiolos causes increased levels of IRF4, which in turn upregulates MYC. Interestingly, IRF4 inhibition is toxic to a wide range of myeloma cell lines, which suggests that this might be an essential survival factor for all subtypes of multiple myeloma and explains the direct cytotoxic effect of immunomodulatory drugs on myeloma cells[72]. In addition, thalidomide-driven Ikaros degradation results in increased IL-2 production in T cells, which causes an increase in the number of functional cytotoxic T cells and partly explains the immunomodulatory action of this type of drug[73,74]. Independent of its ubiquitylation-related function, cereblon was also shown to promote the maturation of the monocarboxylate transporter 1 (MCT1; also known as SLC16A1)–BSG complex, which is involved primarily in lactate export. Lactate export is required for the glycolytic pathway, of which increased use is typical for malignant cells[75,76].

The sensitivity of multiple myeloma cells to bortezomib and other proteasome inhibitors is probably related to the balance between the load and the capacity of the proteasome. Indeed, as plasma cells are antibody-producing cells, they have a physiological induction of the unfolded protein response to accommodate for antibody production[77,78], and, as such, multiple myeloma is sensitive to therapies that increase stress on protein turnover, such as proteasome inhibition. Overexpression of specific proteasome subunits and higher proteasome capacity were linked to resistance to bortezomib[78]. In addition, differentiation plasticity in multiple myeloma cells might be related to bortezomib resistance. Although multiple myeloma cells are generally considered to be a fairly

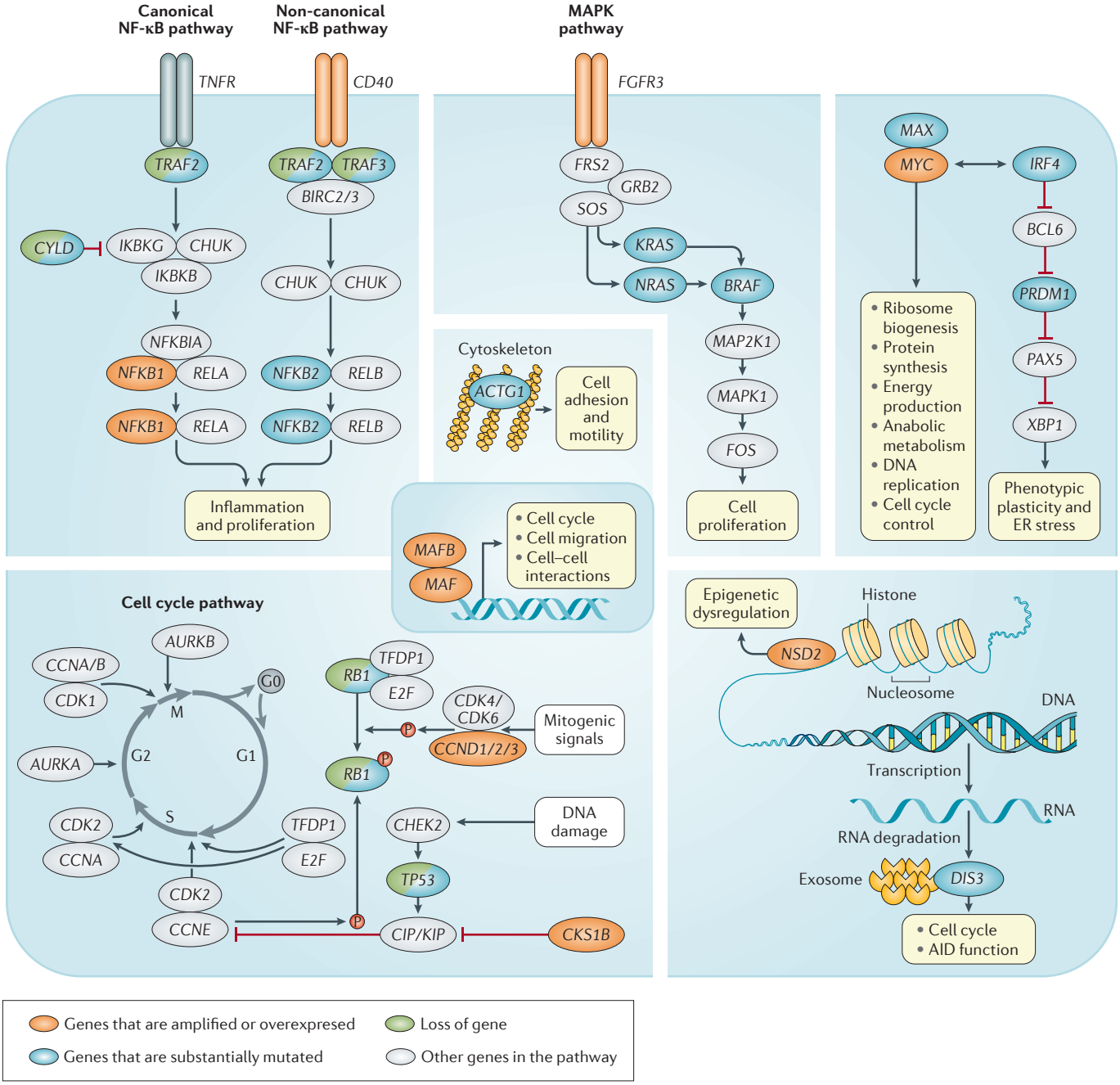

Figure 3 | **Signalling pathways affected in multiple myeloma.** Genetic alterations in multiple myeloma can affect several cellular signalling pathways. Frequent genetic aberrations in patients with multiple myeloma include *MYC* rearrangements, mutations in *KRAS* and *NRAS*, translocation t(11;14) and translocation t(4;14). Several chromosomal translocations indicate a central role of the cyclin D proteins in multiple myeloma; t(11;14) leads to overexpression of *CCND1* (which encodes cyclin D1) and t(6;14) leads to overexpression of *CCND3*. *CCND2* overexpression is also frequently observed in multiple myeloma. Other recurrent mutations include *DIS3*, *TP53*, *BRAF*, *TRAF3*, *PRDM1*, *CYLD*, *RB1*, *MAX* and *ACTG1*, of which (putative) functional links are indicated. Nuclear factor-κB (NF-κB) signalling is a central pathway in B cells, and this pathway is deregulated in most B cell malignancies. As opposed to some other types of B cell malignancies, multiple myeloma is mostly characterized by the activation of the non-canonical NF-κB pathway; alterations that affect the activation of this pathway include overexpression of CD40, mutations and deletions of *TRAF2* or *TRAF3* and mutations in *NFKB2* (also known as *P100*), although aberrations that affect the canonical pathway have also been described, such as *CYLD* mutations. Signalling in the canonical pathways occurs through several receptors, including B cell receptor, Toll-like receptors and tumour necrosis factor receptor (TNFR). Furthermore, for the non-canonical pathway, multiple receptors are involved including CD40 (also known as TNFRSF5), lymphotoxin-β receptor (also known as TNFRSF3) and also TNFR. Several genetic alterations indicate an important role for cell cycle deregulation in multiple myeloma, including overexpression of *CKS1B*, deletion and/or mutation of *TP53* and frequent deletion of *RB1*. Other pathways of interest are the interaction with multiple myeloma cells and the microenvironment through overexpression of *MAF* oncogenes (in patients with t(14;16) or t(14;20)), which results in integrin deregulation. Mutations in *ACTG1* are putatively involved in a cytoskeletal defect. AID, activation-induced cytidine deaminase; ER, endoplasmic reticulum; MAPK, mitogen-activated protein kinase. Adapted with permission from REFS 153,154, Macmillan Publishers Limited.

homogeneous population of terminally differentiated cells, reports such as these point towards a possible role for a subset of multiple myeloma cells with a distinctly different biological behaviour and a capacity to act as a reservoir for relapse[79,80].

Although multiple myeloma cases are genetically variable, it was proposed that essential factors for multiple myeloma development could exist, as all cases share several similarities (such as cell type and morphology). If such a factor exists, it would offer the possibility of

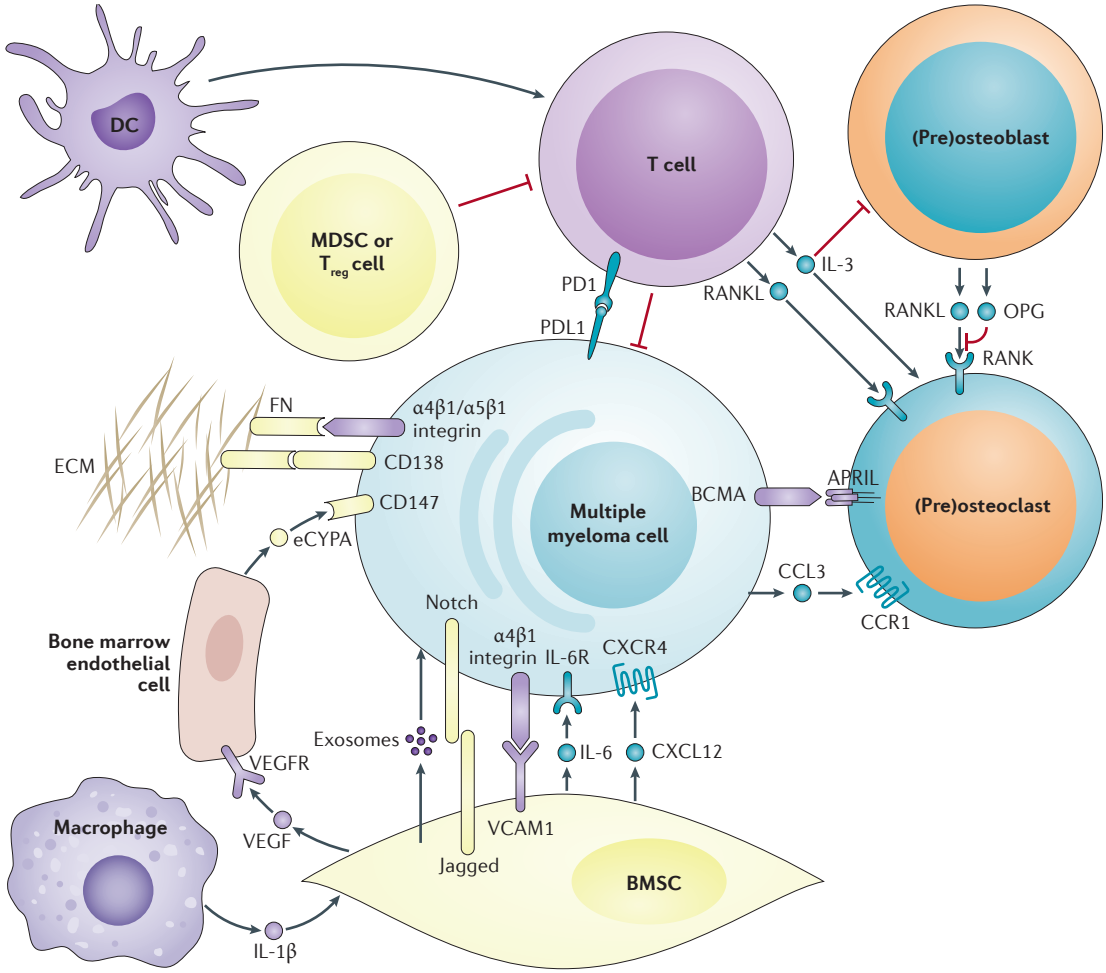

Figure 4 | **Tumour microenvironment.** The most important interactions in the multiple myeloma bone marrow microenvironment are shown, with the exception of recent and interesting findings, such as cyclophilin A and exosomes[62]. Central in the multiple myeloma microenvironment is the bone marrow stromal cell (BMSC), which is instrumental in creating a favourable niche for multiple myeloma growth. Indeed, the physical interaction of vascular cell adhesion protein 1 (VCAM1) on the cell surface of BMSCs and integrin on the myeloma cells results in the secretion of several cytokines, which favour myeloma cell proliferation and inhibit apoptosis[155]. CXC-chemokine ligand 12 (CXCL12; also known as SDF1) is expressed by BMSCs, osteoblasts, endothelial cells and multiple myeloma cells themselves[156]. BMSC-produced CXCL12 binds to CXC-chemokine receptor type 4 (CXCR4) on multiple myeloma cells[157] and is important for the migration of myeloma cells to the bone marrow. Other factors produced by BMSCs include Jagged (which activates Notch on multiple myeloma cells) and vascular endothelial growth factor (VEGF; which promotes angiogenesis). Factors such as receptor activator of nuclear factor-κB ligand (RANKL; also known as TNFSF11) and CC-chemokine ligand 3 (CCL3) are involved in the differentiation of precursor osteoclasts to mature osteoclasts, and are involved in bone destruction in multiple myeloma[158]. Macrophages in the microenvironment produce a wide range of factors, including IL-1β, which act on stromal cells and induce IL-6 (REF. 159). Several cell types, including BMSCs, T cells, B cells, monocytes and multiple myeloma cells, produce IL-6, which promotes proliferation of multiple myeloma cells and resistance to apoptosis[156]. The extracellular matrix (ECM) in the tumour microenvironment consists of several proteins, including fibronectin (FN), laminin and collagen. CD138 (also known as syndecan 1) binds directly to ECM proteins such as fibronectin, which has been shown to confer drug resistance (that is, cell adhesion-mediated drug resistance)[160]. Finally, a proliferation-inducing ligand (APRIL; also known as TNFSF13), which is produced by monocytes and osteoclasts, can result in nuclear factor-κB (NF-κB) activation, among other factors[161]. By expressing programmed cell death 1 ligand 1 (PDL1), multiple myeloma cells negatively affect T cells, which is one of the mechanisms of immune evasion by multiple myeloma cells[156,162]. The anti-myeloma response via dendritic cells (DCs) is partly impaired owing to poor T cell activation capacity[156]. BCMA, B cell maturation antigen; CCR1, CC-chemokine receptor 1; eCYPA, extracellular cyclophilin A; IL-6R, IL-6 receptor; MDSC, myeloid-derived suppressor cell; OPG, osteoprotegerin; PD1, programmed cell death protein 1; RANKL, receptor activator of nuclear factor-κB ligand; T_{reg}, regulatory T cell; VEGFR, VEGF receptor.

Box 3 | **Diagnostic criteria**

The diagnosis of monoclonal gammopathy of undetermined significance (MGUS), smouldering multiple myeloma (SMM) and multiple myeloma requires the detection of serum monoclonal protein levels, assessment of the bone marrow and myeloma-defining events (MDEs; including biomarker assessment and the presence or absence of CRAB features) (see the table).

CRAB features:

- Hypercalcaemia: serum calcium levels of >1 mg per dl higher than the upper limit of normal levels (>11 mg per dl)
- Renal insufficiency: the presence of creatinine clearance of <40 ml per min or serum creatinine levels of >2 mg per dl
- Anaemia: haemoglobin levels of >2 g per dl below the lower limit of normal levels (<10 g per dl)
- Bone lytic lesions: the presence of one or more lytic lesions detected by conventional radiology, CT imaging (or low-dose CT) or PET–CT

MDEs*:

- CRAB features
- A clonal bone marrow plasma cell (BMPC) percentage of ≥60%
- An involved-to-uninvolved serum free light-chain ratio of ≥100
- Two or more focal lesions on MRI

*If there is no end-organ damage, the presence of one or more biomarker is sufficient for diagnosis.

Feature	MGUS	SMM	Multiple myeloma
Serum monoclonal protein levels	<3 g per dl and	≥3 g per dl and/or	–
Clonal BMPC infiltration*	<10%	10–60%	≥10% or a biopsy-proven plasmacytoma‡
Symptomatology	Absence of CRAB features	Absence of MDE or amyloidosis	Presence of MDE

*The clonality of BMPCs has to be established by restriction of the light chain, kappa or lambda, by flow cytometry, immunohistochemistry or immunofluorescence. Assessing the infiltration of these cells into bone marrow should be done by morphology, either in the aspirate or biopsy. ‡If the BMPC infiltration is <10%, more than one lytic lesion is required to confirm a diagnosis of multiple myeloma.

treating all patients with multiple myeloma effectively. Examples of such essential factors in multiple myeloma include IRF4 and caspase 10 (which is involved in regulating autophagy in multiple myeloma cells)[72,81]. Indeed, as previously mentioned, inhibition of IRF4 is toxic to several multiple myeloma cell lines.

Clinical manifestations

As previously mentioned, some of the clinical manifestations of multiple myeloma can be driven by high levels of monoclonal protein production. As a consequence of this, free light chains can accumulate in the kidney. In healthy individuals, light chains are filtered at the glomerulus and reabsorbed at the proximal tubuli. In multiple myeloma, the capacity of this reabsorption is exceeded, which is the cause of light-chain accumulation in the distal segment of the nephron where the light chains can combine with Tamm–Horsfall urinary glycoprotein (also known as uromodulin) and precipitate to form obstructing casts, resulting in renal impairment[82]. The quantity of free light chain is not directly correlated to the occurrence of renal impairment, indicating that differences between light-chain species may contribute to causing this impairment[83]. Patients with multiple myeloma can also develop amyloidosis, which not only affects the kidney but also the heart and other organs. Finally, renal impairment can be caused by hyperviscosity and myeloma cell infiltration[84].

Diagnosis, screening and prevention

The most widely accepted diagnostic criteria are the updated International Myeloma Working Group (IMWG) criteria[5]. Accordingly, diagnosis should be made according to these criteria, which are based on monoclonal protein levels, the bone marrow infiltration of clonal plasma cells, in addition to validated new biomarkers and CRAB features (of which biomarkers and CRAB features are collectively known as 'myeloma-defining events'; BOX 3)[5]. Following diagnosis, some of these tests can also be used to monitor treatment responses. The new biomarkers are based on the level of bone marrow plasma cell infiltration, serum free light-chain (sFLC) level or ratio and the presence of two or more focal lesions on MRI, and can identify patients with SMM who are at imminent risk of progression to active disease[5]. The presence of myeloma-defining events is the main feature that allows multiple myeloma to be distinguished from other plasma cell disorders, such as MGUS or SMM. Additional evaluation might be required to confirm that the CRAB features are attributable to multiple myeloma and not to other comorbidities or concomitant diseases[85].

Diagnostic work-up

Individuals with the multiple myeloma precursor states MGUS and SMM are generally asymptomatic, and these conditions are usually detected incidentally as part of the diagnostic work-up of unrelated conditions[5]. In addition, MGUS and SMM can be detected owing to the presence of an increased erythrocyte sedimentation rate or total protein level in routine blood tests or after noticing protein in the urine.

Patients with multiple myeloma typically present with symptoms related to end-organ damage that result in the diagnosis, including fatigue or dyspnoea related to anaemia, bone pain related to bone disease and neurological symptoms related to hypercalcaemia, hyperviscosity or spinal cord compression (due to spinal lesions)[86]. If patients have concomitant, related conditions such as amyloidosis, symptoms might be related to the organ that contains the amyloid inclusions. The initial investigation of a patient with suspected multiple myeloma includes clinical assessment, measurement of monoclonal protein levels, bone marrow biopsy and radiographic imaging.

Clinical assessment. Clinical assessment for multiple myeloma includes medical and family history, in addition to physical examination. The family history should focus on first-degree relatives with a diagnosis of haematological malignancies, especially lymphoma, chronic lymphocytic leukaemia and plasma cell dyscrasias. Past medical history should focus on comorbidities and concomitant diseases that could affect treatment decisions, such as hypertension, diabetes mellitus and renal disease.

Laboratory testing. A complete blood count with differential should be ordered, including a peripheral blood smear. A complete biochemistry screen should also be performed, which includes liver function tests and renal function tests (including glomerular filtration rate, electrolytes, calcium, creatinine, lactate dehydrogenase and albumin levels). Only renal failure caused by light-chain cast nephropathy is regarded as a myeloma-defining event, and performing renal biopsy to clarify the underlying cause of the renal failure is recommended by the IMWG.

Other laboratory tests include the assessment of β_2-microglobulin and monoclonal protein levels. Levels of β_2-microglobulin are included in the staging systems for multiple myeloma and, as such, are required as part of the diagnostic work-up[85]. In addition, both serum and urine are assessed for monoclonal protein using protein electrophoresis. Serum immunofixation is the optimal method used to both confirm the presence of monoclonal protein and to distinguish its heavy-chain and light-chain types. A 24-hour urine sample should be performed, with protein electrophoresis used to detect and measure the levels of monoclonal protein. Measurement of serum free light-chain levels is also recommended, especially in the case of oligosecretory or non-secretory multiple myeloma (that is, patients who lack secretion of monoclonal protein). However, a subset of patients with non-secretory multiple myeloma have a normal sFLC ratio but with clear multiple myeloma, so the secretion of monoclonal protein is not a required criterion for the diagnosis[5].

Unilateral bone marrow aspirate and/or bone marrow biopsy are also required for the diagnosis of multiple myeloma, and the diagnosis is confirmed if ≥10% of the cells in the bone marrow are clonal plasma cells in the presence of a myeloma-defining event. If both aspirate and biopsy methods are performed, the highest percentage of plasma cells reported is used. The clonality of the bone marrow plasma cells can be evaluated by immunohistochemistry of the bone marrow biopsy (using CD138 (also known as syndecan 1) stains), or alternatively by immunoperoxidase staining or immunofluorescence. Immunophenotyping of the cells using flow cytometry is also possible to identify the clonality.

Radiographic imaging. Bone disease should be evaluated at diagnosis in all patients and in accordance with the new IMWG criteria, and can include the use of new imaging assessments, such as skeletal survey with plain X-rays, CT imaging or ^{18}F-fluorodeoxyglucose PET–CT. However, the exact imaging modality used is determined by availability and resources. The aim is to use more-sensitive techniques, such as CT or PET–CT, to detect bone lesions earlier; indeed, the presence of at least one lesion (>5 mm in size) indicates multiple myeloma. In addition, MRI of the thoracic and lumbar spine and the pelvis, but ideally, whole-body MRI, is required for some patients, such as those with suspected multiple myeloma and the absence of CRAB features, and patients with SMM. However, in other patients with multiple myeloma, MRI is not mandatory. MRI provides detailed information about bone marrow involvement and the presence of focal lesions. Indeed, the presence of more than one focal lesion detected using whole-body MRI in patients with SMM was associated with a significantly shorter median time to progression to multiple myeloma than patients without focal lesions[87,88].

Prognostic factors and risk stratification

Several factors, including the presence of some cytogenetic abnormalities and biomarkers, can act as prognostic factors in patients with multiple myeloma. Cytogenetic markers should be evaluated in the bone marrow of all patients with multiple myeloma[89]; del(17p) and t(4;14) are considered to be the most informative cytogenetic markers in terms of poor prognosis[42,90]. However, the coexistence of other genetic defects might alter the risk profile, as trisomies of chromosome 3 or chromosome 5 (often associated with hyperdiploidy) have been suggested to improve the poor risk associated with del(17p) and t(4;14)[39,90]. Conversely, other defects might contribute to a worsening risk, for example, the presence of del(1p32) in patients with t(4;14) and del(6q) in patients with del(17p)[91]. The good prognosis conferred by t(11;14) might be diminished by the coexistence of del(1p)[92,93].

The risk stratification system by the IMWG stated that t(4;14), t(14;16), t(14;20) and del(17/17p), in addition to any non-hyperdiploid karyotype are considered to be high-risk cytogenetic factors in patients with multiple myeloma, regardless of treatment[94]. Other risk stratification systems consider t(4;14) to be associated with an intermediate risk, given the better outcome in these patients with proteasome inhibitors[93]. Combinations of three or more of any cytogenetic abnormalities confer an ultra-high risk, and are associated with <2 years survival[95]. Routine testing for prognostic factors should include the detection of t(4;14) and del(17p); fluorescence *in situ* hybridization in CD138-positive cells was established as the standard technique in the IMWG consensus, although more-sophisticated procedures, such as gene expression profiling, mutation detection and copy number abnormalities, should be evaluated.

Several risk classification systems for multiple myeloma have been proposed, such as the International Staging System (ISS)[96]. Together with the cytogenetic abnormalities, other laboratory tests are relevant for the assessment of prognosis, including albumin and β_2-microglobulin levels, both of which are the basis for the ISS[96]. Lactate dehydrogenase levels and cytogenetic abnormalities were later added to the classification system, resulting in the revised ISS, which incorporates many of the relevant prognostic factors and distinguishes three subgroups of patients with different prognosis[94,96,97] (BOX 4). In addition, several other prognostic factors have been described that have a varying effect on the survival outcomes[94] (BOX 4). The ISS is not currently used to determine management strategies.

Prevention

For some cancers, risk factors that provide an opportunity for prevention have been identified. However, with multiple myeloma, some risk factors that might influence

the risk of disease have been identified, but most of them, such as advanced age, male sex, African-American race or family history, are not preventable.

Progression from MGUS to multiple myeloma. Multiple myeloma is consistently preceded by the precursor state MGUS, which has been detected in 4% of white individuals ≥50 years of age and ~5% of individuals ≥70 years of age[7]. Although most MGUS cases are never diagnosed and only a small proportion progress to a malignant disorder, data from one group indicated that prior knowledge of MGUS had a significant and positive effect on the overall survival of patients with multiple myeloma, which was probably related to the clinical follow-up[98]. In addition, patients with MGUS who had lower levels of monoclonal protein (<0.5 g per dl) at diagnosis had poorer survival than patients who had monoclonal protein levels between 0.5 and 3 g per dl (REF. 98). The authors of the study speculate that this might be reflective of current guidelines, which suggest less-frequent monitoring of patients with MGUS who have lower concentrations of monoclonal protein[98]. These findings are consistent with those of another, smaller study[99]. Patients with MGUS should be stratified according to the risk of progression to multiple myeloma, and risk factors, such as isotype, monoclonal protein concentration, sFLC ratio and immunoparesis must be evaluated[100]. However, these studies confirm the importance of lifelong follow-up for patients with MGUS, independent of risk score, and probably reflect the need for better risk models based on the biology of the disease.

Progression from SMM to multiple myeloma. As previously mentioned, some patients with multiple myeloma might have an identified phase of SMM (FIG. 1), an intermediate stage between MGUS and multiple myeloma, that is most frequently suspected in a routine analysis but without a uniform risk of progression to multiple myeloma over time. The annual risk of progression from SMM to multiple myeloma is 10% per year for the first 5 years, 5% per year during the subsequent 5 years and then 1% per year after 10 years[9].

Several groups have identified possible predictors of progression from SMM to symptomatic multiple myeloma, which could be useful for physicians and can help to explain to patients their risk of disease progression. Indeed, the first step in clinical practice is to identify the risk of progression to multiple myeloma for each newly diagnosed patient with SMM (BOX 5). Two models of progression, the Mayo Clinic and Spanish models, have been validated in a prospective trial, but newer risk models that incorporate novel clinical and biological features are emerging[101]. The components of these models are not identical, and each patient's risk of disease progression should be defined on the basis of all the available data rather than through the use of a restricted model. Not all risk factors have to be present in a patient with SMM for the patient to be defined as high risk of progression. The clinical definitions have recently been updated to include ultra-high-risk SMM as multiple myeloma, and the exact biological differences are under ongoing investigation[5].

Box 4 | **Risk stratification**

International Staging System

Stage I: serum β_2-microglobulin levels of <3.5 mg per litre and serum albumin levels of ≥3.5 g per dl

Stage II: not stage I or stage III

Stage III: serum β_2-microglobulin levels of ≥5.5 mg per litre

Revised International Staging System

Stage I: International Staging System stage I, normal lactate dehydrogenase (LDH) levels and standard risk cytogenetic markers, detected using fluorescent *in situ* hybridization (FISH)

Stage II: not stage I or stage III

Stage III: International Staging System stage III and either higher than normal LDH levels or high-risk cytogenetic markers, detected using FISH (such as the presence of del(17p), t(4;14) and t(14;16))

Other prognostic factors

- Circulating plasma cell numbers
- Extramedullary disease
- High plasma cell proliferative rate
- High-risk gene expression signatures (GEP70 and HOVON, among others)
- Presence of *TP53* mutations
- Renal failure
- Poor performance status
- Immunoparesis
- Plasmablastic morphology

In patients with high-risk SMM, early treatment might prolong the time to development of multiple myeloma. Indeed, one phase III randomized trial showed a significantly longer median time to progression to multiple myeloma in patients with high-risk SMM who underwent early treatment with lenalidomide and dexamethasone, than patients who received observation only, after a median follow-up of 40 months[102]. After a median follow-up of 75 months, progression to multiple myeloma was significantly higher in patients in the observation group (86%) than in patients who received lenalidomide and dexamethasone treatment (39%). In addition, median overall survival from the time of study entry had not been reached in either group, but the reduced progression rate with the early treatment had been sustained after long-term follow-up[103]. This study showed for the first time the potential for changing the treatment paradigm for patients with high-risk SMM based on the efficacy of early treatment in terms of time to progression to multiple myeloma and of overall survival, confirmed after long-term follow-up. Several other trials are underway to investigate the role of novel agents, such as lenalidomide alone, siltuximab (an anti-IL-6 monoclonal antibody), elotuzumab (an anti-SLAMF7 (signalling lymphocytic activation molecule family member 7) monoclonal antibody) or lenalidomide, dexamethasone plus elotuzumab in patients with high-risk SMM. Promising results have been reported for the combination of lenalidomide, dexamethasone and carfilzomib in a series of 12 patients with high-risk SMM; all patients achieved a complete response[104]. The next step will be

to develop a more-intensive therapeutic approach for patients with high-risk SMM, like the treatment planned for young symptomatic patients with multiple myeloma, for whom a cure should be the objective.

Promising biomarkers are being evaluated and will be incorporated in the future to the multiple myeloma criteria; these biomarkers include multiparametric flow cytometry, high numbers of circulating plasma cells, specific cytogenetic abnormalities, genomic markers and increasing levels of monoclonal protein as well as decreasing levels of haemoglobin during the course of the disease.

Management

The overall approach to the treatment of multiple myeloma has undergone several changes during the past decade, which has been driven by a better understanding of the disease biology, the availability of several very effective classes of drugs, and a focus on the role of supportive care and QOL.

Initial therapy

The initial choice of treatment for multiple myeloma needs to consider several factors (FIG. 5). The initial goals of therapy include rapid and effective control of multiple myeloma, reversing the complications of, or symptoms related to, multiple myeloma, and enable the collection of stem cells in patients who are eligible for ASCT.

Transplant eligibility. The treatment strategy in multiple myeloma has historically hinged on whether the patient is ASCT eligible, as some drugs, such as melphalan, can impede the ability to collect stem cells[105]. As treatments have become safer with less haematological toxicity, an increasing convergence of the treatment approaches for transplant-eligible and transplant-ineligible patients has occurred, and, in the future, this might have limited influence on treatment selection[93]. At present, transplant eligibility remains a substantial factor in deciding the initial therapy, and substantial differences exist in who is considered transplant eligible (FIG. 5).

Pharmacological therapy. The therapeutic armamentarium in multiple myeloma has continued to improve, with several classes of effective drugs available for the management of newly diagnosed and relapsed myeloma (BOX 6). One of the early improvements in the treatment of multiple myeloma was the demonstration of the deleterious effect of high doses of steroids that were used as part of the early treatment regimens[106]. The improved survival seen with weekly dose of dexamethasone, despite inferior response rates than pulse-dose approach that used three-times higher steroid doses, made this the standard dosing approach for dexamethasone as part of various combinations.

The combination of a proteasome inhibitor and immunomodulatory drug is currently one of the most effective approaches in patients with newly diagnosed multiple myeloma. Indeed, the use of bortezomib in combination with lenalidomide and dexamethasone (that is, VRd) is considered the initial treatment of choice for all patients who are able to tolerate a multidrug combination (FIG. 5). This is based on results from a large phase III trial, which showed an improvement in progression-free survival and overall survival in patients with newly diagnosed multiple myeloma, following VRd, compared with patients who received lenalidomide and dexamethasone only[107]. Other combinations of proteasome inhibitors and immunomodulatory drugs, such as bortezomib, thalidomide and dexamethasone, have been evaluated, and patients treated with this combination showed an improved progression-free survival but no improvement in overall survival compared with thalidomide and dexamethasone, but all patients also received an ASCT following the initial therapy[108]. Proteasome inhibitors have also been studied in combination with alkylating agents, such as melphalan and cyclophosphamide, as initial therapy in transplant-ineligible patients. The combination of bortezomib, cyclophosphamide and dexamethasone has shown excellent tolerability and high-efficacy rates in several phase II trials[109]. In one phase III study, bortezomib, cyclophosphamide and dexamethasone was compared with bortezomib, thalidomide and dexamethasone in preparation for ASCT and demonstrated inferior response rates but a reduced incidence of clinically relevant neuropathy[110]. Ongoing trials are evaluating the replacement of bortezomib with carfilzomib in these combinations, based on promising early results. One of these three regimens should be considered for initial therapy in patients who are eligible for ASCT, based on the availability of the individual drugs and the reimbursement available (insurance coverage).

In patients who are ineligible for ASCT, treatment approaches have sought to build on the melphalan and prednisone regimen. Immunomodulatory drugs, such as thalidomide and lenalidomide, as well as bortezomib have been combined with melphalan and prednisone

Box 5 | **Classification of patients with smouldering multiple myeloma**

Patients with smouldering multiple myeloma (SMM) should be classified according to the risk of disease progression to multiple myeloma.

Low risk

These patients are characterized by the absence of the high-risk factors (such as serum monoclonal protein levels of ≥30 g per litre; the presence of non-IgG monoclonal protein and serum involved/uninvolved free light-chain (FLC) ratio of ≥8 (but <100), among other factors) (using the validated Mayo or the Spanish risk models), with a probability of progression at 5 years of only 8%. The patients in this group behave similarly to patients with monoclonal gammopathy of undetermined significance (MGUS) and should be followed annually.

Intermediate risk

These patients only display some of the high-risk factors and are probably patients with true SMM. They have a risk of progression at 5 years of 42%, and they must also be followed up probably every 6 months (except during the first year, which should be followed up every 3–4 months to exclude an evolving multiple myeloma).

High risk

Half of high-risk patients will progress during the 2 years following diagnosis. These patients need a close follow-up every 2–3 months. If possible, the best approach should be to refer them to specialized centres in multiple myeloma therapy, and to include them in clinical trials to better understand their biology and to confirm the survival benefit of early treatment in this cohort.

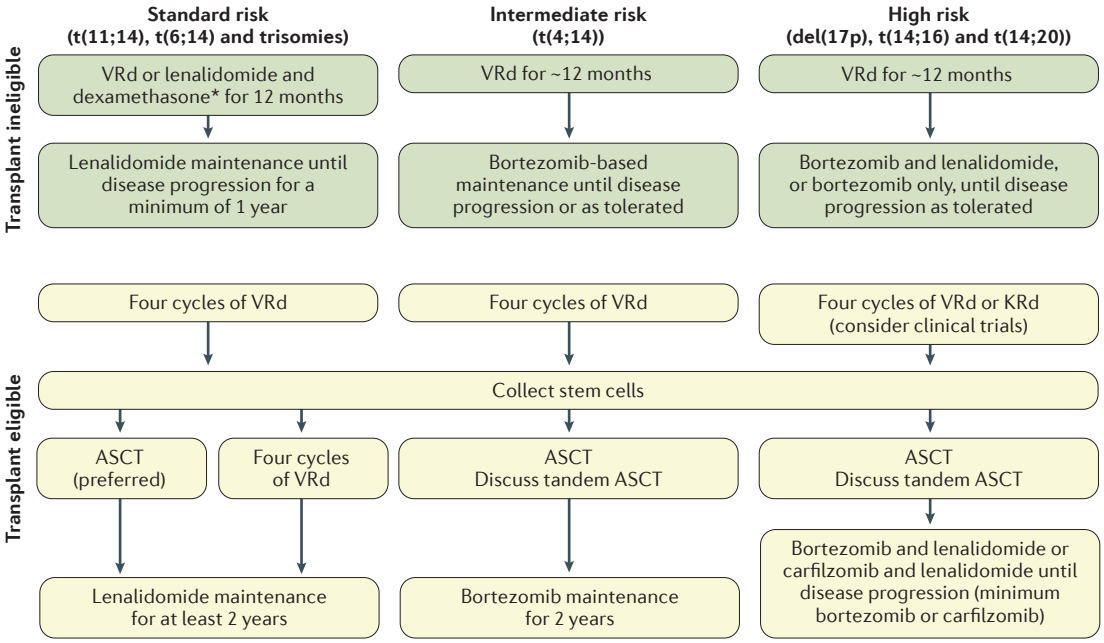

Figure 5 | **Suggested algorithm for the management of multiple myeloma.** Several factors can determine the management strategy for multiple myeloma, including whether the patient is eligible for autologous haemopoietic stem cell transplantation (ASCT). Age has been the main determinant of eligibility for ASCT, with most randomized trials limiting this to patients ≤65 years of age[116,117,163]. However, several studies have demonstrated similar outcomes with ASCT in older patients, and it is likely that the physiological age is more relevant than the chronological age[164]. The second main determinant is the presence of comorbidities; a more uniform agreement exists, which indicated that patients with substantial comorbidities, such as cardiac and pulmonary disorders, should not be offered ASCT, although this might be altered based on the experience of the centre. Renal insufficiency, including the need for chronic haemodialysis, does not have to limit the use of ASCT, especially as one-third of the patients with multiple myeloma might present with some degree of renal insufficiency[164]. Finally, patient preference plays a substantial part in determining the use of ASCT. Other factors that determine the course of treatment include the age of the patient, their ability and/or desire to undergo ASCT, the risk stratification, performance status and the presence of comorbidities that might increase the toxicity of therapy. KRd, carfilzomib, lenalidomide and dexamethasone; VRd, bortezomib in combination with lenalidomide and dexamethasone. *Denotes treatment for patients who are ≥75 years of age or are frail.

in phase III trials that have demonstrated improved progression-free survival compared with the use of melphalan and prednisone[111–113]. Although these triplet drug combinations have become the standard initial approach in multiple myeloma, particularly among patients who are transplant ineligible, doublet drug combinations have a role in selected groups of patients. For example, in the FIRST trial, transplant-ineligible patients who received lenalidomide and dexamethasone until disease progression demonstrated improved overall and progression-free survival compared with patients who received melphalan, prednisone and thalidomide; as such, the lenalidomide and dexamethasone combination remains an excellent treatment option for patients who are older and more fragile[114]. Treatment approaches for patients who are ineligible for transplantation need modification based on patient characteristics, including age, performance status and frailty metrics; although these factors might not necessarily limit the use of triplet drug combinations, doses must be reduced for all drugs in these combinations depending on the patient status. The European Myeloma Network has put forward an excellent algorithm for adapting treatment approaches for these patients[115].

ASCT. ASCT was introduced as a consolidation approach in multiple myeloma over two decades ago and has been demonstrated to provide improved overall survival in several phase III trials[116–118]. To prepare for ASCT, patients undergo peripheral blood stem cell collection with growth factor support (granulocyte colony-stimulating factor treatment) with or without chemotherapy, followed by myeloablative conditioning and reinfusion of collected stem cells. Typically, ASCT has been used after 4–6 cycles of initial therapy (that is, induction therapy) and has been shown to improve the depth of response translating into improved response duration[116–118]. There has been increasing debate on the role of ASCT in the current era with the high efficacy of the new drug regimens, but several phase III trials have demonstrated enhanced responses and improved overall and progression-free survival with the use of ASCT[118]. With the increasing use of post-ASCT interventions, such as consolidation and maintenance strategies, ASCT is considered an integral component of a multistep treatment programme rather than a stand-alone treatment strategy. Meta-analysis of several phase III trials clearly demonstrates an improved overall survival in patients treated with lenalidomide maintenance therapy

Box 6 | **Currently used drugs in multiple myeloma**

Proteasome inhibitors
- Bortezomib
- Carfilzomib
- Ixazomib

Immunomodulatory drugs
- Thalidomide
- Lenalidomide
- Pomalidomide

Monoclonal antibodies
- Daratumumab (anti-CD38)
- Elotuzumab (anti-SLAMF7 (signalling lymphocytic activation molecule family member 7))

Histone deacetylase inhibitor
- Panobinostat

Alkylating agents
- Melphalan
- Cyclophosphamide
- Bendamustine

Others
- Dexamethasone
- Prednisone
- Cisplatin
- Etoposide
- Doxorubicin

following ASCT, compared with patients who received ASCT only, although its benefit in high-risk patients seems to be limited[119–121]. Although several trials have demonstrated a progression-free survival advantage for tandem ASCT compared with single ASCT, improvement in overall survival has not been consistent, and its role in the current therapy of multiple myeloma remains undefined[122]. Studies have also suggested an increase in overall survival with the use of tandem ASCT compared with a single ASCT in patients with high-risk genetic factors, such as del(17p) and t(4;14)[123]. Ongoing trials will continue to define the role of ASCT, especially in the setting of routine post-transplantation consolidation and maintenance.

Duration and goals of therapy

The overall approach to the treatment of multiple myeloma, especially in terms of treatment goals and the duration of therapy to achieve these goals, has changed over time. Two key developments have changed the treatment strategies: newer drugs such as proteasome inhibitors and immunomodulatory drugs that have less cumulative toxicity and that can be given for long periods of time, and the effect of a deep response on survival outcomes coupled with the introduction of minimal residual disease (MRD) testing[124].

The use of maintenance therapy has become commonplace in both transplant-eligible and transplant-ineligible patients. Among patients undergoing ASCT, lenalidomide maintenance therapy has been shown to improve progression-free survival and overall survival, following ASCT in a meta-analysis of several phase III trials[121]. Bortezomib has also been studied in the phase III setting, albeit not independently of its addition to the induction and consolidation therapy[123]. Given the preponderance of data, maintenance therapy post-ASCT is considered the standard of care, with consideration given to the use of bortezomib in patients with high-risk multiple myeloma.

Several studies and meta-analysis have shown that achievement of deep responses, such as stringent complete response (a lack of monoclonal protein detected in the serum and urine, <5% clonal plasma cell infiltration into the bone marrow and a normal sFLC ratio) and MRD negativity (no monoclonal protein in the serum or urine and a clonal plasma cell infiltration into the bone marrow of <1 in 10^5), following treatment of multiple myeloma results in improved progression-free survival and overall survival[125]. Although the data do not support change in therapy in a given patient to achieve MRD, application of regimens with the highest likelihood of MRD negativity can result in improved survival. Indeed, in another analysis of several phase III trials, an improvement in the progression-free survival and overall survival was seen with continuous lenalidomide therapy compared with a fixed-duration therapy in the non-transplant setting[126]. Although a longer duration of therapy than that used with the older approach improves outcomes, the ideal duration of therapy remains debated and is probably determined by the risk status of the patient.

Management of relapsed disease

Most patients with multiple myeloma will eventually relapse and need additional therapies; a suggested algorithm for the management of these patients is shown in TABLE 1. As patients go through multiple relapses, the efficacy of salvage regimens is reduced, which is associated with a reduced duration of responses, highlighting the development of drug refractoriness[127]. This reduction in efficacy is driven by the increasing genomic complexity of the tumours and the acquisition of a myriad of mutations and epigenetic alterations, and highlights the need for new classes of drugs with different mechanisms of action[48]. To this end, several new drug classes are being explored in clinical trials, many of which seem to be promising (TABLE 2).

Several factors should be considered when confronted with relapsed disease, including the presence of CRAB features, risk stratification and the presence of specific genetic abnormalities. Patients do not need to be immediately restarted on therapy with the earliest evidence of biochemical progression of multiple myeloma, as many patients have a very slow rate of increase in the levels of monoclonal protein, especially after ASCT[128]. However, if patients have new evidence of CRAB features, the need for therapy is clear. Other factors that indicate therapy should be initiated include patients with high-risk disease, a rapid increase in the levels of monoclonal protein, high levels of sFLC (especially in patients with renal manifestations at presentation) and patients who present with neurological

complications at initial diagnosis. Patients with an isolated plasmacytoma as the only manifestation of relapse can often be managed with focused radiotherapy to the single lesion and then observed closely[129]. As previously mentioned, risk stratification is also relevant for deciding the course of treatment in patients with relapsed disease, and many of the risk factors from diagnosis are likely to be applicable in this setting as well, as are the ISS stage and cytogenetics. In addition, the duration of the initial therapy is a strong prognostic factor; patients with primary refractory disease or disease progression within 18 months of starting initial therapy generally have poor outcomes[130]. The choice of salvage regimens must take into account the risk status of the patient, prior treatment regimens used and the sensitivity to those drugs, previous adverse events, as well as residual toxicity from prior therapy, prior use of ASCT, performance status and patient wishes.

Symptomatic management

In addition to management of the malignant cells, patients with multiple myeloma might require treatment of the underlying symptoms of this disease, such as bone disease, anaemia and pain. Regarding the bone lesions in patients with multiple myeloma, bisphosphonates can delay the progression of lytic bone lesions and prevent fractures[131], whereas vertebroplasty (that is, injecting bone cement into a fractured vertebrae) and balloon kyphoplasty (a minimally invasive surgery used to align broken vertebrae into their correct position) are standard procedures to control pain in patients with vertebral fractures[132]. Radiotherapy can also be effective for pain associated with vertebral fractures[133]. Pain should be assessed regularly at all stages of the disease, and, if detected, treatment should start with non-opioid analgesics, avoiding the use of NSAIDs owing to the risk of renal failure[134]. Opioid analgesics should be added when needed to achieve optimal pain control. Prevention of the expected adverse effects associated with analgesics, especially constipation with opioid use, is essential. Specific pain syndromes, such as neuropathic pain (which is frequently related to treatment), can benefit from the use of antidepressants or anticonvulsants[135]. Fatigue is also common in patients (75% of patients) and is mainly related to anaemia and can sometimes be worsened by treatment[136]. Transfusions might be necessary to treat the anaemia; erythropoiesis-stimulating agents are recommended at the lowest dose possible to avoid transfusion, with adequate iron and vitamin support[131].

Patients with multiple myeloma have a high risk of infections, as a result of the disease, the treatment and the presence of comorbidities[137]. The most frequent causes of infection in patients with multiple myeloma are *Streptococcus pneumoniae*, *Haemophilus influenzae* and Gram-negative bacilli[138]. Antibiotic prophylaxis can be helpful at least during the first 3 months of treatment, and antiviral prophylaxis is mandatory in patients receiving proteasome inhibitors, given the risk of herpetic infections with these drugs[131]. Intravenous immunoglobulins might be useful in patients with severe recurrent bacterial infections and in case of severe immune deficiency[131].

Quality of life

Patients with multiple myeloma often report substantial impairment in health-related QOL (HRQOL). Indeed, some of the most frequent features of multiple myeloma can affect QOL from diagnosis onwards, including bone disease and anaemia[134], of which, bone disease is present in up to 90% of patients[139]. The improvement in patient survival with newer therapeutic agents, such as immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies with favourable risk–benefit profiles, have made HRQOL an increasingly important end point in clinical trials and a factor in treatment decisions[140]. Recent data show that novel effective treatment options can improve QOL without any effect on HRQOL[141], but many patients live with the burden of the disease and treatment-related adverse events, such as infections and neuropathy, particularly in the late stages of the disease[119–121].

Table 1 | **Therapies for relapsed multiple myeloma**

Current therapy	Fit patients*	Frail patients
Patients who are on maintenance therapy		
Thalidomide	Bortezomib, carfilzomib, ixazomib, elotuzumab, or daratumumab combined with lenalidomide	Lenalidomide, bortezomib, carfilzomib, ixazomib, or daratumumab with dexamethasone‡
Lenalidomide	Bortezomib, carfilzomib, ixazomib, elotuzumab, or daratumumab combined with pomalidomide§ or daratumumab with bortezomib	Bortezomib, carfilzomib, ixazomib, or daratumumab with dexamethasone‡
Bortezomib	Carfilzomib, elotuzumab, or daratumumab combined with lenalidomide	Lenalidomide, carfilzomib, or daratumumab combined with dexamethasone‡
Patients who are off therapy		
NA	Bortezomib, carfilzomib, ixazomib, elotuzumab, or daratumumab combined with lenalidomide and dexamethasone or daratumumab with bortezomib	Doublets of lenalidomide, bortezomib, ixazomib, carfilzomib, or daratumumab with dexamethasone‡

NA, not available. *Consider salvage autologous haemopoietic stem cell transplantation (ASCT) in patients who are eligible for ASCT who have not had a transplantation before; consider a second ASCT if the patient is eligible and >18 months unmaintained or >36 months maintained response to the first ASCT. ‡Triplet drug combinations, as with fit patients, can also be considered with adequate dose reductions. §Only phase II studies are available for these regimens.

Table 2 | **New drugs in clinical trials**

Drugs	Mechanism	Phase	ClinicalTrials.gov identifier
Small molecules			
Filanesib, pomalidomide and dexamethasone	Kinesin spindle protein inhibitor	I–II	NCT02384083
Marizomib, pomalidomide and dexamethasone	Proteasome inhibitor	I–II	NCT02103335
Selinexor, carfilzomib and dexamethasone	Inhibition of nuclear export protein	II	NCT02628704
Ricolinostat, bortezomib and dexamethasone	Histone deacetylase 6 inhibitor	II	NCT01323751
Melflufen and dexamethasone	Alkylating agent	II	NCT02963493
Venetoclax, bortezomib and dexamethasone	Inhibition of BCL2	III	NCT02755597
Immune therapies			
MOR202	Anti-CD38 monoclonal antibody	I	NCT01421186
Durvalumab, pomalidomide and dexamethasone	PDL1 checkpoint inhibitor	I–II	NCT02616640
Nivolumab	Anti-PD1 checkpoint inhibitor	I–II	NCT03023527
CD19 CAR T cells	CD19	I–II	NCT02135406
BCMA CAR T cells	BCMA	I–II	NCT02658929
Pembrolizumab and dexamethasone	Anti-PD1 checkpoint inhibitor	III	NCT02576977 and NCT02579863
Isatuximab	Anti-CD38 monoclonal antibody	III	NCT02990338

BCMA, B cell maturation antigen; CAR, chimeric antigen receptor; PD1, programmed cell death protein 1; PDL1, programmed cell death 1 ligand 1.

In the cure and comfort model, supportive care (also called palliative care) plays an essential part from diagnosis to end of life. Palliative care improves the QOL of patients and their families who are facing the problems of life-threatening illnesses, through the prevention and relief of suffering by the early identification, assessment and treatment of pain and other physical and psychosocial issues. If palliative care relieves symptoms while patients are receiving chemotherapy in the early stages of disease, in the late stage, when the disease can no longer be treated, palliative care does not alter disease progression, but it helps patients to live as active as possible, and their family to cope with the illness and the bereavement. The goal is to achieve control of pain and other symptoms that might cause distress. Timely, collaborative care, with fluid communication between the haematologists, the palliative care physicians, the family physicians, the patients and their family is essential, integrating the medical, psychological and psychosocial aspects of care. Importantly, a longitudinal and continuous care should be provided[137].

Outlook

Substantial strides have been made in our journey towards control and possibly cure of different cancers, and the progress in the treatment of multiple myeloma, and, consequently, the improvement in patient survival has been profound. Application of cutting-edge genomic technologies has unravelled the underlying biology to an extent that allows us to contemplate the individualization of therapies[34,46]. However, much work needs to be done, as the majority of patients continue to relapse and a substantial minority continues to have little benefit from the recent advances. Several specific areas need to be addressed if we are to continue to make progress in this disease.

Treatment response and new therapies

Nearly one-quarter of patients with multiple myeloma attain short duration of treatment responses with some of the most effective drug regimens, and have a median overall survival of ~3 years[90]. Although some of the known prognostic factors, such as genomic abnormalities, can predict the clinical course, a substantial proportion of these patients do not have identifiable high-risk features at diagnosis. As such, more work needs to be done to identify these patients ahead of time, so that newer and different therapeutic approaches can be studied. Some early steps have been made, by discovering gene expression signatures that identify high-risk patients as well as mutation panels that can evaluate for new mutations. Continued work in this area will need to address the tumour microenvironment in patients with multiple myeloma and its contribution to the clinical phenotype of disease. In particular, the immune profile of patients might have a crucial role in the clinical behaviour, a hypothesis that is strongly supported by the success of the immune-based therapies. Emerging technologies, such as single-cell sequencing and mass cytometry, can play an important part in deciphering the individual contribution of the different cell types. Understanding these factors will also help us to develop specific treatment strategies for these patients, where the current approaches are continuing to fail.

One of the most exciting therapeutic advances in multiple myeloma has been the introduction of immune therapies, including monoclonal antibodies, checkpoint inhibitors and T cell-based therapies. Daratumumab, a monoclonal antibody that targets CD38 on the multiple myeloma cell surface, has, in combination with immunomodulatory drugs or proteasome inhibitors, resulted in MRD-negative responses in patients

with relapsed disease[142–144]. Several new antibodies are currently in development, including those conjugated with various toxins. The results with chimeric antigen receptor (CAR) T cells, although early, have elicited substantial enthusiasm. In particular, CAR T cells as well bi-specific T cell engagers utilizing B cell maturation antigen as the target are starting to enter clinical trials, and the early results should become available in the near future (TABLE 2). These therapeutic approaches in turn have turned the focus back on the immune system in multiple myeloma, and, as we understand more about the state of the immune system, more advances are sure to follow.

Advances in therapy have also brought to the fore the disadvantages of the response criteria, which are limited to measuring the levels of monoclonal protein and evaluating the bone marrow using tests that are of low sensitivity[124]. The IMWG have revised the uniform response criteria to include definitions of MRD in multiple myeloma, which can be tested using sequencing or flow cytometry-based approaches[124]. In addition to examining the bone marrow, PET–CT imaging has been incorporated into the response criteria to rule out any extramedullary disease[124], but this still requires repeated bone marrow examination, and ongoing studies are examining the feasibility of performing molecular studies on peripheral blood, which will allow for repeated sampling. Progress is being made in the quantification of circulating multiple myeloma cells as well as cell-free DNA from the tumour cells. Although the relationship between MRD and survival has been clear for some time and has been further confirmed by a meta-analysis[125], which has facilitated its use as a surrogate end point in clinical trials, in the clinic, use has been limited to prognosis. The next generation of clinical trials will ask the important question of whether making a clinical decision based on MRD status, such as changing therapy, intensifying therapy or discontinuing therapy, will alter outcomes, but this cannot be recommended at present in the absence of prospective data.

An area that is going to see substantial progress in the coming decade is the concept of early intervention. For decades, we have been aware of the precursor stages of multiple myeloma, including SMM, which has a high risk of transformation to active multiple myeloma. For several reasons, including the toxicity of drugs, the cost, the effect on QOL and most importantly the lack of a survival benefit for early treatment, therapeutic intervention was only instituted for the development of CRAB features. With the most recent revision of the IMWG diagnostic criteria, the presence of biomarkers that predict a high risk of progression (about ≥80% in 2 years) have been added to the myeloma-defining criteria, thus crossing that barrier of treating an asymptomatic individual[124]. The increasing availability of safe and highly effective drugs, and studies that have shown an improvement in overall survival in patients with high-risk SMM, following early treatment, have created immense interest in exploring early treatment approaches[102].

The concept of early intervention to prevent disease progression from SMM to multiple myeloma has also raised the hypothesis that, combined with the use of intensive multidrug combinations that are used in active disease, might provide a realistic opportunity at eradicating the malignant clone and potentially 'curing' the disease. Clinical trials are being designed to ask this question, but will take a long time to complete. Until then, surrogate markers, such as MRD negativity, that are persistent over several years, will provide early signals if these are indeed a possibility. On the other extreme, some patients do not survive relapsed disease, for whom new therapeutic options are essential. Ongoing studies trying to unravel the mechanism of drug resistance and to identify new drug classes are underway. Several new drug classes are in clinical investigation, including selective histone deacetylase inhibitors, immunotherapy and drugs that target the altered metabolic pathways, among others. Continued success will depend on a multipronged approach that will continue the search for the elusive cure while simultaneously targeting the disease biology to develop new treatment options.

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Author contributions
Introduction (S.K.K.); Epidemiology (R.A.K.); Mechanisms/pathophysiology (P.S. and M.v.D.); Diagnosis, screening and prevention (M.-V.M.); Management (V.R. and S.K.K.); Quality of life (F.G.); Outlook (K.C.A.); Overview of Primer (S.K.K.).

Competing interests
S.K.K. has served as a consultant for Takeda, Amgen, AbbVie, Merck, Janssen and Skyline Dx. K.C.A. is a member of the advisory board for Millennium Pharmaceuticals, Bristol-Myers Squibb and Gilead Sciences, and is a Scientific Founder of OncoPep and C4 Therapeutics. R.A.K. serves on the disease monitoring committees for Celgene, Bristol-Myers Squibb, Onyx Pharmaceuticals (Amgen) and Pharmacyclics. P.S. is an adviser for Amgen, Bristol-Myers Squibb, Celgene, Janssen, Takeda and Skyline Dx, and has received research support from Amgen, Celgene, Janssen and Takeda. F.G. serves as an adviser for Celgene, Takeda, Roche, Seattle Genetics and Amgen, and has received honoraria from Celgene, Janssen, Amgen, Bristol-Myers Squib and Takeda. M.-V.M. is a consultant for Amgen, Celgene, Janssen and Takeda, and has received speaker's fees from Janssen, Celgene, Amgen and Takeda. V.R. and M.v.D. declare no competing interests.

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