Seminar

Multiple myeloma

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Multiple myeloma is a malignant disease of plasma cells that manifests as one or more of lytic bone lesions, monoclonal protein in the blood or urine, and disease in the bone marrow. Treatment for myeloma has changed beyond recognition in the past decade, and now includes state of the art supportive treatment and infusional chemotherapy courses, followed for younger patients by high-dose melphalan and an autologous transplant. Patients younger than 70 years can now expect a doubling of median survival to 5 years, a 20% chance of surviving longer than 10 years, and a 50% chance of attaining complete morphological and biochemical remission. Bisphosphonate control of bone disease is essential. Exploitation of the understanding of the biology of myeloma has led to the development of biological treatments, such as thalidomide, CC-5013, and bortezomib, which target the myeloma cell and the bone-marrow microenvironment, which plays a crucial part in the disease's pathogenesis. These treatments will hold the key to future success.

Multiple myeloma is a disorder in which malignant plasma cells accumulate, generally derived from one clone in the bone marrow.[1] Intricate interactions occur between the bone-marrow microenvironment and the myeloma cells, frequently causing bone destruction, which in turn stimulates tumour growth.[2] The tumour itself, its products, and the host response to it result in the multitude of symptoms and organ dysfunction characteristic of myeloma, including bone pain, renal failure, susceptibility to infections, anaemia, and hypercalcaemia. Until the early 1980s, myeloma caused a slow progressive decline in quality of life until death after about 2 years.[3] This pattern changed in the early 1980s after the observation that one high dose of an alkylating agent could produce a clinical state in which, by ordinary macro (non-molecular) means, the disease disappeared—ie, a state of complete remission.[4,5] Thus, with modern treatments, the complete remission rate is 20–59%, with a median overall survival of 4·4–7·1 years and a median event-free survival of 24–43 months.[5–23] A proportion of these patients have continued in first complete remission for more than 10 years.[24] Research in myeloma is evolving rapidly, with 10–15 new biological agents entering phase I–III studies. This seminar is about these changes.

Incidence

The median age at diagnosis is 68 years. Myeloma accounts for 1% of all malignant disease in white populations and 2% in black populations, and 13% and 33%, respectively, of all haematological cancers.[25] The incidence in the USA is around four per 100 000 general population each year. Men are more frequently affected than women. The incidence is higher in black people and lower in Asians than in white people.[25]

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Biology of myeloma

Substantial advances have been made to our understanding of the biology of myeloma leading to new treatments that have been developed that target the myeloma cell, myeloma cell-host interaction, and the bone-marrow microenvironment.

Assessment of malignant plasma cells and pathogenesis

Multiple myeloma is a B-cell neoplasm and myeloma cells are the transformed counterparts of postgerminal-centre bone-marrow plasmablasts or plasma cells. Multiple oncogenic events have been identified that have contributed to the pathogenesis of myeloma.[26] Figure 1 describes the molecular pathogenesis of myeloma in detail.[26]

Because of the many DNA breaks necessary for immature B cells to become mature plasma cells, B cells already have inherent genetic instability. DNA breaks are necessary for VDJ recombinations, somatic mutations, and isotype switching. Therefore, genetic alterations frequently occur at the Ig heavy-chain site at 14q32, which is abnormal in around 75% of myeloma patients.[26]

Search strategy and selection criteria

We searched for published reports on PubMed and MEDLINE, the website of Science Direct, and the websites of the journals *Blood*, *Journal of Clinical Oncology*, *New England Journal of Medicine*, and *The Lancet*. We also browsed the CD-roms (published as supplement for Blood) from the meeting of American Society of Hematology in 2000–03 to look at interesting and clinically relevant presentations. The key words we used were "Multiple Myeloma", "therapy", "randomized", "biology", "transplantation", "conventional therapy". No limits were set for search criteria, although papers published between 1995 and 2003 have been preferentially included. We consulted the text book *Myeloma* (Mehta J, Singhal S, eds; London: Martin Dunitz, 2002). We gave preference to randomised and other studies published in peer-reviewed journals with an impact factor of more than 2. We excluded case reports and articles that were not published in English.

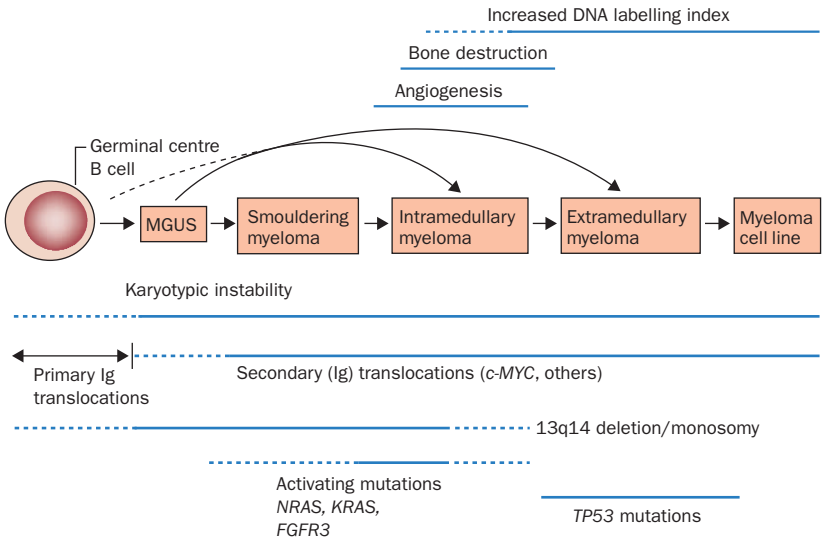

Figure 1: **Molecular pathogenesis of myeloma: multiple oncogenic events**

Myeloma cells have a low proliferative potential, hence conventional cytogenetic methods (giemsa or G-banding) detects chromosomal alterations in 30–50% of cases. In patients with rapidly dividing myeloma cells (high labelling index or aggressive disease),[27] however, detection of cytogenetic abnormalities is easier. With the use of fluorescent in-situ hybridisation, which allows direct analysis of specific DNA sequences in non-dividing cells, and the use of chromosome painting, such as multicolour fluorescent in-situ hybridisation and multicolour spectral karyotyping, chromosomal abnormalities may be defined in most cases.[28–30] Abnormalities of chromosome 13 (–13 or 13q [figure 2]) and hypodiploidy have been associated with poor survival. Figure 2 also shows t(4;14), which, along with t(14;16), and p53, deletion have also become of interest and carry a poor prognosis.[31–33]

Bone-marrow microenvironment and cytokines

The bone-marrow microenvironment consists of extracellular matrix proteins, bone-marrow stromal cells, vascular endothelial cells, osteoblasts, osteoclasts, and lymphocytes. The interactions of the myeloma cells with the extracellular matrix proteins and bone-marrow stromal cells, along with the factors in the marrow microenvironment such as cytokines and angiogenesis, play an important part in the pathogenesis of myeloma.[34–37]

Adhesion of myeloma cells to fibronectin confers protection from apoptosis, whereas binding of myeloma cells to bone-marrow stromal cells induces transcription and secretion of cytokines, including interleukin 6, insulin-like growth factor-1 (IGF-1), and tumour necrosis factor α (TNF α), vascular endothelial growth factor (VEGF), and stroma-derived factor-1.[34]

Interleukin 6 (MAPK)

Interleukin 6 is a major growth and survival factor for myeloma cells. It triggers proliferation via the Ras, Raf, MEK, mitogen-activated protein kinase cascade. This cytokine protects against dexamethasone by PI3/AKT signalling and activation of the SH2 domain, containing protein tyrosine phosphatase. Interleukin 6 promotes myeloma-cell survival via phosphorylation of signal transducer and activator of transcription 3 and up-regulation of antiapoptotoc molecules, such as Mcl-1, Bcl-x_L and c-Myc. Interleukin 6 induces VEGF expression and secretion in myeloma cells and inhibits antigen-presenting function of dendritic cells, hence contributing to the immumocompromised status characteristic of myeloma.[34]

IGF-1

This growth factor is secreted by bone-marrow stromal cells. It increases growth, survival, and drug resistance in myeloma cells by activating *Ras* and mitogen-activated protein kinase, and the PI3K and Akt pathways, phosphorylation of BAD (BCL2 family member; pro-apoptotic protein), and inhibition of apoptosis.[34]

VEGF

Interleukin 6 induces VEGF expression and secretion in myeloma cells. VEGF triggers growth and migration of myeloma and plasma-cell leukaemia cells, augments interleukin 6 produc-

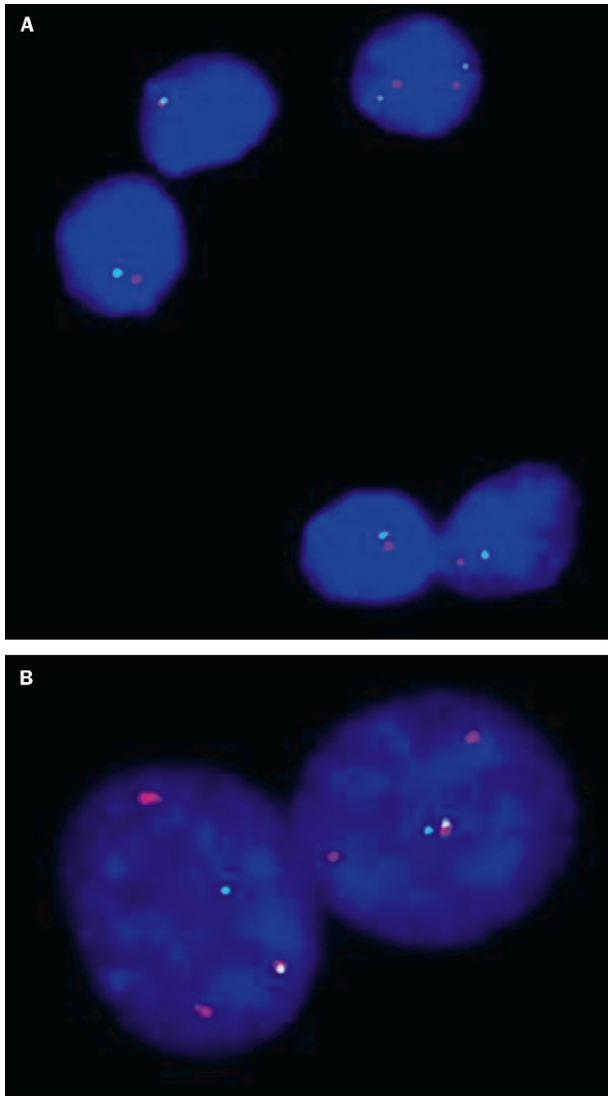

Figure 2: **Fluorescence-in-situ hybridisation showing deletion of two probes on chromosome 13 (A) and fusion between probes for FGFR3 and IgH (B), indicating t(4;14)**

tion in bone-marrow stromal cells, and stimulates marrow angiogenesis, which is increased in some myeloma patients.[34] It activates MAPK signalling and low-level myeloma-cell proliferation and migration of myeloma cells mediated by protein kinase C. VEGF, like interleukin 6, also inhibits the antigen-presenting function of dendritic cells contributing to immunocompromised status.

TNF α and nuclear factor κ B

TNF α is produced by myeloma cells and bone-marrow stromal cells and its secretion is substantially higher in myeloma patients with bone disease than in those without bone disease. Nuclear factor κ B (NF-κB) is also an attractive target in the marrow milieu since it regulates expression of adhesion molecules on myeloma cells and bone-marrow stromal cells and regulates cytokine production. Increased NF-κB activity is associated with increased tumour-cell survival in myeloma.[34,35] TNF α activates NF-κB and up-regulates expression of adhesion molecules such as very-late antigen-4 and leucocyte-function-associated antigen 1 on myeloma cells and their ligands vascular-cell adhesion-molecule 1 and intracellular adhesion molecule 1 on bone-marrow stromal cells and increases binding of myeloma cells to bone-marrow stromal cells, hence promoting myeloma-cell survival and protection against apoptotic stimuli.[36] Newer agents target both NF-κB and TNF α.[34,35]

Stroma-derived factor 1

Stroma-derived factor 1 promotes proliferation, induces migration, and partially protects against dexamethasone-induced apoptosis in myeloma cells. Stroma-derived factor 1 also increases secretion of interleukin 6 and VEGF in bone-marrow stromal cells and functions as a chemoattractant, which localises myeloma cells in the marrow microenvironment.[34]

Interleukin 1β and osteolysis

Interleukin 1β is produced mainly by bone-marrow stromal cells and induces interleukin 6 production in myeloma cells and activates osteoclasts and bone resorption. Several other osteoclast-activating factors such as parathyroid-hormone-related protein, hepatocyte growth factor, and TNF α are generated by interaction of myeloma cell with bone-marrow stromal cells.[38] Two mechanisms are important for osteolysis. The first involves macrophage inflammatory protein 1α secreted by myeloma cells and functions as osteoclast chemotactic and maturation factor.[39] The second involves a receptor activator of NF-κB (RANK) that binds the cytokine NF-κB-receptor-activator ligand and is a key pathway for osteoclastogenesis. Bone-marrow stromal cells produce osteoprotegerin, which prevents excessive activation of osteoclasts by serving as a decoy receptor and competing with NF-κB-receptor activator for binding to the NF-κB-receptor-activator ligand (RANKL).[34,39]

Signalling cascades and drug resistance

Myeloma cells, in the early stages of the disease, are completely dependent for their survival and proliferation on the marrow microenvironment, which also causes resistance to chemotherapy (epigenetic resistance). In the marrow microenvironment, the myeloma cells acquire major genetic alterations described above, which allow them to become stroma-independent (hence extramedullary disease) and resistant to chemotherapy (genetic resistance), leading to the transformation stage of the disease.[40]

The lack of apoptosis in myeloma cells is due to up-regulation of antiapoptotic factors (bcl-x_L, mcl-1, bcl-2), up-regulation of inhibitors of apoptosis and resistance to apoptosis induced by FAS and TNF-related apoptosis-inducing ligand.[41,42] These antiapoptotic mechanisms are induced by cytokines and ligands in the microenvironment. Although myeloma is sensitive initially to treatment, drug resistance is acquired in most cases. An association has been reported between cumulative treatment with vincristine and doxorubicin and the expression of multidrug-resistance gene and p-glycoprotein expression in tumour cells.[43] The adhesion of myeloma cells to fibronectin via β1 integrins in the marrow microenvironment is associated with a cell-adhesion-mediated drug resistance.[44]

The apoptotic signalling cascades have been identified in myeloma cells to allow novel treatments to trigger death pathways. For example, IGF-1 activates two distinct signalling pathways, mitogen-activated protein kinase and phosphoinositol 3-kinase, leading to proliferative and antiapoptotic effects.[45] Concerning the death pathways for the myeloma cell, FAS, TNF-related apoptosis-inducing ligand, γ radiation, and thalidomide, with its analogues, activate caspase 8, whereas dexamethasone and arsenic trioxide (As_2O_3) activate caspase 9; proteasome inhibitor bortezomib activates both caspases 8 and 9. In all cases, downstream death signalling is mediated via activation of caspase 3.[46–50] Use of two agents that have different death pathways can be additive or synergistic for treatment in patients with myeloma.

Myeloma cells are endowed with a multiplicity of antiapoptotic signalling mechanisms, which accounts for their acquired resistance to current chemotherapy. A better understanding of the signalling pathways, including the use of gene array, will give rise to treatment strategies to overcome drug resistance and triggering apoptosis.

Gene profiling

The chromosomal abnormalities described in myeloma are complex, with the involvement of on an average of seven different chromosomes, and are informative in only about 30% of cases. Because of this multiplicity of changes, establishing correlations between genetic abnormalities and clinical outcomes has been difficult.[51,52] The use of high-density oligonucleotide DNA microarray has made possible a simultaneous analysis of messenger RNA expression patterns of thousands of genes. Zhan and colleagues[51] published gene-expression profiles of malignant plasma cells and included comparisons with normal plasma cells that were sorted from normal tissues, which provided a comprehensive global gene expression profile of newly diagnosed myeloma patients and contrasted these expression patterns with those of normal plasma cells. Tarte and colleagues[53] have also provided a novel gene profile comparison of malignant and normal plasma cells from individual patients.

Of 50 myeloma-associated genes, five cancer and testis-tumour antigen genes were noted in a subset, and represent potential tumour-specific therapeutic targets. At least five genes have been identified as primary, non-random translocation partners. These genes include *BCL1*, *PRAD1*, cyclin D1 (11q13), cyclin D3 (6p21), *FGFR3-MMSET* (4p16.3), *C-MAF* (16q23), and *MAFB* (20q11).[54–56] Deletions of chromosome 13 are also common and appear early in the disease course.[57] During the ensuing progression of the disease, additional karyotypic instability develops and mutations or dysregulation in expression of genes such as *CMYC*, *NRAS*, *KRAS*, *FGFR3*, and *P53* occur.[26]

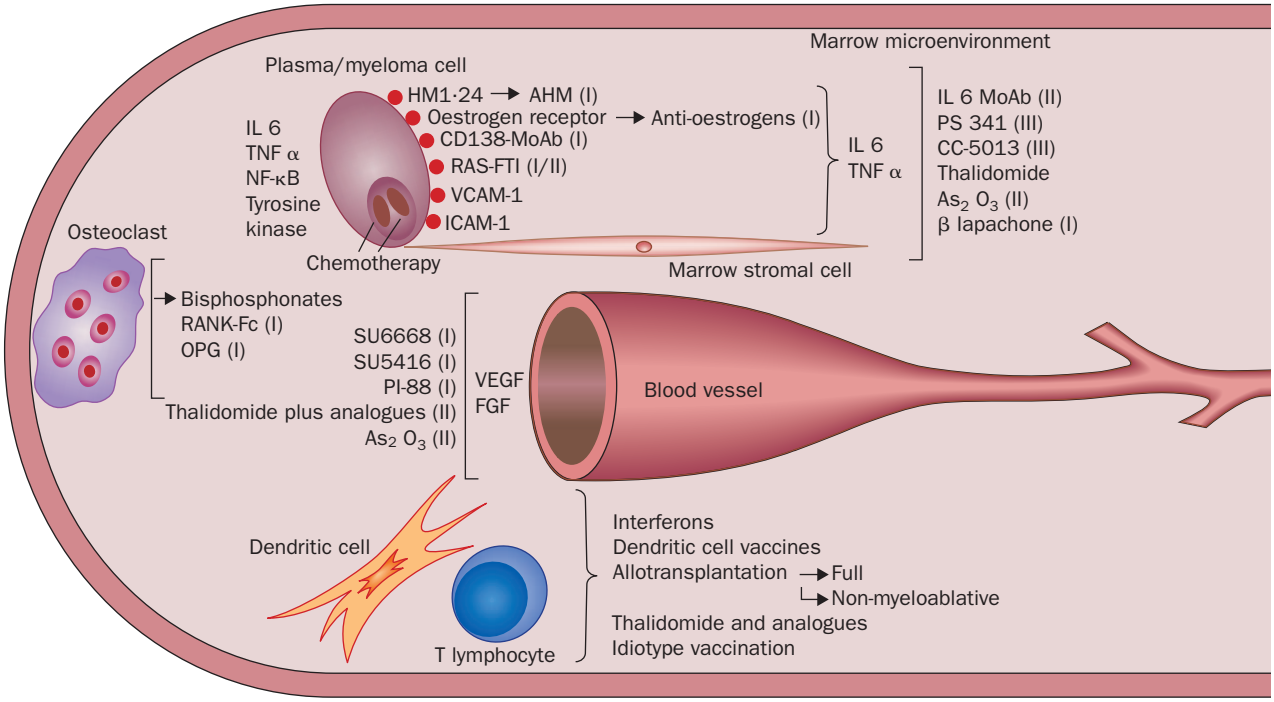

Figure 3: **Targets for antimyeloma treatment**

Phase of testing shown in parentheses. IL 6=interleukin 6. FGF=fibroblast growth factor. OPG=osteoprotenegrin. ICAM-1=intracellular adhesion molecule-1. VCAM-1=vascular cell adhesion molecule-1. RANK Fc=monoclonal antibody to receptor activator of NFκB ligand. FTI=farnesyl-transferase inhibitors. As_2O_3=arsenic tri-oxide. MoAb=monoclonal antibody.

Gene-expression profiling with the use of high-density oligonuceotide microarray will allow molecular classification of myeloma and help to identify new drugs that act specifically on particular biochemical and genetic pathways. The Myeloma Gene Index and myeloma-gene-enriched microarray represent useful resources for investigators interested in dissecting the molecular basis of this disease.[51,58]

Understanding these molecular mechanisms is important because they provide potential therapeutic targets for the identification of new drugs (figure 3). So far, we have focused on chemotherapy and its capacity to destroy myeloma cells, but the new treatment strategies aim to target drug therapy at the growth and apoptotic signalling cascades in myeloma cells, the marrow microenvironment, and to improve allogeneic and autologous immunity to myeloma and the genetic abnormalities in myeloma cells.

Clinicopathological features of patients with myeloma

Patients with myeloma might be diagnosed by chance through screening for other reasons, although they generally present with infections, bone symptoms, or renal failure, and have one or more of a monoclonal paraprotein or light chain (in serum or urine), bone lesions, and bone-marrow infiltration with malignant plasma cells.[59] These and other laboratory investigations make the diagnosis of myeloma and its complications which are listed in table 1. The panel describes some of the common presenting symptoms that require treatment within 24 h of diagnosis.

Myeloma cells can proliferate as solitary plasmacytoma or in a premyelomatous condition, detectable, perhaps for years, only as an isolated finding of a monoclonal paraprotein in the serum termed monoclonal gammopathy of unknown significance (MGUS).[60] Monoclonal gammopathy of unknown significance is the most frequent clonal plasma-cell disorder in the general population, and it transforms into multiple myeloma in 25–30% of patients.[60–62] Smouldering myeloma is a loose term for disorders half way along the spectrum between monoclonal gammopathy of unknown significance and florid myeloma.[59] Another rare variant of myeloma is plasma-cell leukaemia, defined as an absolute plasma-cell count in the blood of more than 5×10^9/L, and might

	What to look for
Site and test	
Blood	
Serum immunoelectropheresis and immunofixation	Paraprotein or "M" component 53% IgG, 20% IgA and rarely IgM
Immunoglobulin profile	Immunoparesis
β_2 microglobulin	High (>2·5 mg/L)
Serum free-light-chain assay	Altered κ:λ ratio
Haematology	Low platelet and haemoglobin concentrations, high ESR, plasma cells in peripheral blood
Biochemistry	High creatinine, urea, uric acid, LDH, C-reactive protein, and calcium
Urine	
Immunoelectropheresis and immunofixation	Bence-Jones (20% light chain disease)
Bone marrow	
Aspirate	Plasma cells, morphology, cytogenetics, FISH
Trephine	Cellularity, amyloid , MVD (angiogenesis)
Bones	
Skeletal survey	Lytic lesions, fractures
DEXA scan	Osteoporosis, bone healing
CT/MRI/PET	If needed for plasmacytomas
Whole body	
Serum amyloid protein (SAP)	Amyloid load scan

ESR=erythrocyte sedimentation rate. LDH=lactate dehydrogenase. FISH=fluorescence in-situ hybridisation. MVD=microvascular density. DEXA: Dual energy X-ray absorptiometry.

Table 1: **Investigations to aid diagnosis of multiple myeloma**

Presenting symptoms and treatment during the first 24 h of diagnosis of myeloma

Sepsis or pneumonia
Parenteral broad spectrum antibiotics

Renal failure
Renal replacement therapy by haemofiltration or dialysis

Marrow failure
Consider erythropoietin

Hyperviscosity
Plasmapheresis

Hypercalcaemia
Hydration, bisphosphonates (pamidronate or zoledronate), or steroids

Cord compression
Surgical decompression and consider radiotherapy

Pathological fracture
Adequate analgesia, surgical stabilisation

Vertebral body collapse
Consider vertebroplasty or kyphoplasty

Chemotherapy should be started sooner rather than later in all these situations.

present primarily or develop secondarily in patients undergoing treatment. Treatment is similar to that for patients with myeloma.[63] Differentiating features between these entities are described in table 2.[59–63]

Protein chemistry

The standard protein assessment of myeloma consisted of using agarose gel or cellulose acetate electrophoresis, but this has now been replaced by the more reproducible and faster capillary zone electrophoreses.[64] The heavy-chain (IgG, A, D, or E) and light-chain isotypes (κ or λ) are identified by immunoelectrophoreses or immunofixation. 24 h urine light-chain assays monitor disease progress. IgG occurs in 53% of patients, IgA in 25%, IgD in 1%, and 20% of patients will have only light chains (light-chain myeloma). Non-secretory myeloma occurs in 1% patients.[25,65] β-2 microglobulin is a low-molecular-weight protein that is an independent prognostic factor for survival in most published studies.[15,19,27,66]

Staging

25 years ago, when myeloma patients had few treatment options, Durie and Salmon[67] devised a staging system to predict outcome with measurement of haemoglobin, paraprotein concentration, and renal and bone disease, which worked well. With modern treatment producing complete remissions, however, those prognostic factors are no longer valid.[66] New staging systems have so far depended on single-centre studies showing age, β-2 microglubulin, deletion of chromosome 13, labelling index, immunological subtype of myeloma, C-reactive protein, lactate dehydrogenase, albumin, and several other factors as having roles, but no coordinated multicentre group using modern treatments has optimally used these factors in a Cox's multivariate analysis of independent variables.[15,27,31,66,68] The International Myeloma Foundation has started a worldwide collaboration for a proposed international prognostic index.

Concept of complete remission

Modern treatments for patients with myeloma are aimed at obtaining complete remission, although long-term survival is possible with some evidence of persistent disease, as evidenced by a small serum M protein, unlike leukaemia, in which complete remission is an absolute prerequisite for long-term survival. Complete remission is important because it is a surrogate marker of quality of life, and is an independent prognostic factor for survival.[6,66,69–71] The definition of complete remission has been refined since its first description 20 years ago,[4] and is currently absence of monoclonal paraprotein in serum and urine by immunofixation maintained for a minimum of 6 weeks, less than 5% plasma cells in bone-marrow aspirate and trephine biopsy, no increase in number or size of lytic bone lesions and disappearance of soft-tissue plasmacytomas.[72] Immunofixation rather than immunoelectrophoreses is a central prerequisite because of its reproducibility, sensitivity, and prognostic significance.[73]

Initial or induction chemotherapy for new patients

Oral melphalan was first used to treat myeloma nearly 50 years ago, and in combination with prednisolone has become the standard treatment for some (generally elderly) patients ever since. The response rate is 40–60% but no patients go into complete remission and median survival is 24–30 months.[74] Various combination chemotherapy regimens, including continuous infusions of vincristine and adriamycin, have been developed but show no survival advantage over melphalan and prednisolone. In a meta-analysis including 6633 patients from 27 randomised trials combination chemotherapy was compared with melphalan and prednisolone.[75] Although the

	Monoclonal gammopathy of unknown significance	Solitary plasmacytoma	Smouldering (before treatment)	Multiple myeloma	Plasma-cell leukaemia
Characteristic					
Serum paraprotein	IgG <35 g/L IgA <20 g/L Bence-Jones protein <1 g/day	Present in 50% of cases	>30 g/L	Variable concentration	Variable concentration
Marrow plasma cells	<10%	<5%	>10%	>10%	40–95%
Bence-Jones Proteinuria	Rare	Might be present	Maybe	50% cases	75–90%
Immuneparesis	Rare	Rare	Maybe	>95% cases	Most
Lytic bone lesions	Absent	Present (solitary)	Absent	Present	Present
Anaemia	Absent	Absent	Absent	80%	80%
Renal dysfunction	Absent	Absent	Absent	25% cases	75%
Hypercalcaemia	Absent	Absent	Absent	20%	40%
Symptoms	Absent	Local bone pain	Absent	Frequent	Frequent
PCLI	<0·5%	<1%	<1%	>1%	>1%
Treatment	None, observe 4-6 monthly	Radiotherapy with regular follow-up	None, observe closely monthly	Aggressive treatment	Aggressive treatment

PCLI=plasma cell labelling index.

Table 2: **Differentiating features of monoclonal gammopathy of unknown significance, solitary plasmacytoma, smouldering myeloma, myeloma, and plasma-cell leukaemia**

response rates were significantly higher with combination therapy (60 *vs* 53%, p<0·0001), survival did not differ.[75]

Stem-cell-sparing regimens such as vincristine, adriamycin, and dexamethasone (VAD), or cyclophosphamide, vincristine, adriamycin, and methylprednisolone (CVAMP) are commonly used as induction therapy. Regimens are comprised of vincristine 1·6 mg plus doxorubicin 9 mg/m^2 daily as continuous infusion over 4 days and methylprednisolone 1·5 g intravenously or orally for 5 days or dexamethasone 40 mg on days 1–4, 9–12, and 17–20, with or without cyclophosphamide (known as VAD, VAMP, or CVAMP). The number of courses given ranges from three to five in various studies, and up to 25% of patients are in complete remission at the end of such treatment, although the proportion is 5–8% with the new criteria of complete remission.[15,66,76,77]

Dexamethasone alone can induce rapid responses, with a response rate of 43% and overall survival similar to that for VAD combined.[78] Other regimens being tested as induction therapy are thalidomide in combination with dexamethasone, and idarubicin with dexamethasone.[79,80]

Regimens and approach to the patients differ dependent on whether a patient would be a candidate for a stem-cell transplant. Because of rapid responses, VAD or CVAMP are frequently used as remission-induction before stem-cell transplantation.

High-dose chemotherapy

Once patients have attained maximum response to initial treatment, a different strategy is required to obtain further disease control because relapse occurs sooner rather than later without further treatment. Historically, 30% of new patients will achieve complete remission after one mid-dose of melphalan (140 mg/m^2) without stem-cell rescue, and will remain in complete remission for a median of 3 years.[4,70] The combination of induction treatment with high-dose melphalan can produce an additive effect, especially with a 200 mg/m^2 dose of melphalan, because harvested peripheral blood stem cells can be used as rescue.[81] These cells can be collected with granulocyte-colony-stimulating factor during the recovery phase after high-dose cyclophosphamide or granulocyte-colony-stimulating factor alone. Cyclophosphamide has the disadvantage of substantially higher toxic effects.[82]

In practice, the standard type of treatment now given to myeloma patients younger than 70 years is induction therapy followed by high-dose melphalan (200 mg/m^2) with peripheral blood stem cells as rescue (single or tandem autotransplant in which the first high dose is followed by another within 2–4 months). The treatment-related mortality with an autotransplant is less than 3%, and this procedure is being extended to patients older than 70 years and younger patients with renal failure.[5,15,83,84] Figure 4 shows the overall survival of 451 patients receiving single autotransplantation with 200 mg/m^2 melphalan as consolidative therapy. Median survival is 6·9 years for patients with β-2 microglobulin 2·3 mg/L or less (43% of patients).[19]

Table 3 describes the results of autotransplantation in randomised and non-randomised studies of patients with myeloma.[5–23] The questions that we need to ask are as follows:

What are the evidence-based data to support this treatment?

Attal and colleagues[6] were the first to address this question. In the Intergroupe Francais du Myelome 90 (IFM90) trial[6] they enrolled 200 patients who were randomly assigned conventional chemotherapy alone for 12 months or conventional chemotherapy followed by autotransplant. High-dose treatment significantly improved the response rate (38 *vs* 14%, p<0·001). Data from longer follow-up also show that high-dose treatment significantly improved event-free survival (p=0·01) and overall survival (p=0·03).[85] Four other randomised studies have been done to address the same question. In the British Medical Research Council Myeloma VII trial[7] survival benefit was seen for high-dose treatment.[7] Palumbo and colleagues[8] compared combined melphalan and prednisone with two courses of melphalan 100 mg/m^2 and autotransplant. With high-dose treatment, the complete remission rate, overall survival, and event-free survival were significantly better than with conventional treatment.[8] Fermand and colleagues[9] showed no significant difference in overall survival between conventional and high-dose chemotherapy, although the results of high-dose group were similar to those for the high-dose group in the IFM90 trial. 17 patients in the conventional chemotherapy group received autotransplant at relapse. Blade and colleagues' study[10] differed from the others in that only patients who responded to initial chemotherapy were randomised. At a median follow-up of 66 months, high-dose treatment significantly increased the complete remission rate, although it had no impact on event-free survival and overall survival.[10] Overall, autotransplants, which have a treatment-related mortality of less than 3%, do have benefit.

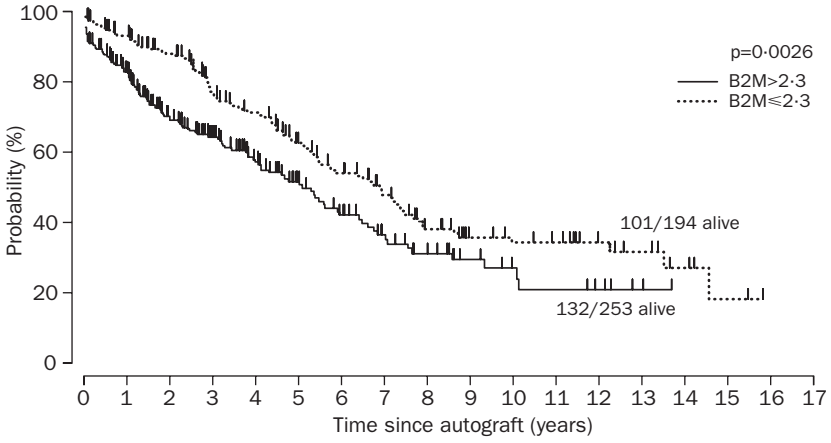

Figure 4: **Logrank comparison of overall survival of patients who received one autotransplantation with 200 mg/m^2 and β2 microglobulin >2·3 mg/L *vs* β2 microglobulin ≤2·3 mg/L**
β2 microglobulin missing in four patients.

Melpahlan 200 mg/m^2 is the most widely used treatment for autografting, and in one randomised study it was the optimum regimen.[86] The addition of total body irradiation to melphalan decreases the outcome significantly because of its side-effects.[86]

Whether high-dose treatment should be done immediately after induction or at relapse was assessed by Fermand and colleagues.[87] They showed that patients who were autografted early had better event-free survival, longer symptom-free periods or time without treatment, and better quality of life. Median event-free survival in the early high-dose group was 39 months, whereas in the late high-dose treatment group median

	Median age (years)	Proportion in complete remission (%)	Median overall survival (months)	Median event-free survival (months)
Study				
Attal et al, 1996 (n=200)[6]*	57			
One transplant	..	22	57	28
Conventional treatment	..	5	44	18
p	..	<0·001	0·03	0·01
Child et al, 2003 (n=407)[7]*	<65			
One transplant	..	44	54·1	31·6
Conventional treatment	..	8	42·3	19·6
p	..	..	0·04	<0·001
Palumbo et al, 2003 (n=195)[8]*	<70			
One transplant	..	29	62	28
Conventional treatment	..	6	43	16
p	..	<0·001	<0·001	<0·001
Fermand et al, 1999 (n=190)[9]*	(55–65)			
One transplant	..	..	55	24
Conventional treatment	..	..	50	19
p	..	..	>0·05	..
Blade et al, 2003 (n=164)[10]*	56			
One transplant	..	30	65	42
Conventional treatment	..	11	67	33
p	..	0·002	>0·05	>0·05
Fermand et al, 1993 (N=63)[11]				
One transplant	44	20	59	43
Haroussaeu et al, 1995 (n=133)[12]				
One transplant	52	37	46	33
Vesole et al, 1996 (n=496)[13]				
One transplant	50	36	41	26
Powles et al, 1997 (n=195)[5]				
One transplant	52	53	54	25
Allegre et al, 1998 (n=259)[14]				
One transplant	52	51	36 (50%)	36 (35%)
Barlogie et al, 1999 (n=231)[15]†				
Two transplants	51	41	68	43
Björkstrand et al, 2001[16]‡				
One transplant (n=1380)	..	..	67	..
Two transplants (n=441)	..	..	85	..
Desikan et al, 2001,[17,18]				
Two transplants (n=1000)	53	44	60 (40%)	60 (25%)
Two transplants (n=515)§	..	..	84 (31%)	84 (18%)
Sirohi et al, 2002 (n=451)[19]				
One transplant	53	59	68·4	28·0
			60 (57%)	60 (31%)
			84 (42%)	84 (20%)
Attal et al, 2003 (n=399)[20]*†	52			
One transplant	..	34	48	25
			84 (21%)	84 (10%)
Two transplants	..	35	58	30
			84 (42%)	84 (20%)
p	..		0·01	0·03
Cavo et al, 2002 (n=220)[21]*				
One transplant	NA	21	56	25
Two transplants	NA	24	60	34
p	..		>0·05	0·05
Fermand et al, 2001 (n=193)[22]*				
One transplant	NA	42	27 deaths	41 events
Two transplants	NA	37	22 deaths	43 events
p	..	..	>0·05	>0·05
Segeren et al, 2003 (n=261)[23]*	55			
One transplant¶	..	13	50	21
Two transplants||	..	29	47	22
p	..	p=0·002	p=0·41	p=0·28

NA=not available. *Randomised. †Intention-to-treat analysis. ‡Matched-pair analysis. §Subset of 1000 patients transplanted 5 years before date of analysis. ¶Patients received melphalan 140 mg/m2 given in two 70 mg/m^2 doses without stem-cell rescue; ||Patients received same regimen as one-transplant group plus cyclophosphamide 120 mg/kg and total-body irradiation at 9 Gy.

Table 3: **Results of autotransplantation given as consolidative treatment for patients with multiple myeloma**

time from randomisation to death or standard treatment failure was 13 months.[87]

Are two transplants better than one?

At first sight it seems obvious that if one transplant is good, two (tandem) transplants must be better. Tandem transplants in sequence were introduced in late 1980s by Barlogie and colleagues.[88] They showed that patients who did not enter remission after the first transplant could achieve remission after the second. In a large non-randomised study, a sequential increase in complete-remission rate was reported after induction with VAD, followed by one and then a second transplant.[15] In another retrospective registry study, tandem transplants led to a small but significantly better survival rate than one transplant (median 85 *vs* 67 months).[16] So far, only one randomised study by Attal and colleagues[20] has been completed. 403 patients younger than 60 years were randomly assigned one autotransplant with melphalan 140 mg/m^2 and total-body irradiation at 8 Gy or tandem autotransplants, the first prepared with melphalan 140 mg/m^2 and the second with melphalan and total-body irradiation. All patients initially received three cycles of VAD. Complete-remission rate did not differ between the two groups, but overall and event-free survival were significantly better with tandem transplants than one transplant at a median follow-up of 5 years. The survival advantage became clear after a longer follow-up, which suggests that tandem transplants are better for low-risk patients.

In the Bologna 96 trial,[21] preliminary analysis at a median follow-up of 3 years showed a significant benefit with tandem transplants for event-free survival, although no difference was seen for overall survival. In this study, tandem transplants conferred a significantly longer median duration of remission than one transplant (44 *vs* 25 months, p=0·005). Two other randomised studies are trying to answer the same question but follow-up is still short.[22,23] Fermand and colleagues[22] have at a median follow-up of 27 months shown no significant benefit for tandem transplants.[22] Segeren and colleagues' study[23] is different, since the single-transplant patients receive melphalan (140 mg/m^2 given in two doses of 70 mg/m^2) without stem-cell rescue; patients in the tandem-transplant group receive the same regimen followed by cyclophsophamide plus total body irradiation with stem-cell rescue. At a median follow-up of 27 months, overall and event-free survival did not differ between the two groups. The conditioning regimen used in this study is not the most optimum regimen.

Biological-immunological treatments

Full *allogeneic* bone-marrow transplantation

The possibility that cancer is controlled by an immune reaction in human beings was noted after graft-versus-host disease was seen to be associated with reduced relapse rates in leukaemia.[89] A similar observation has been made in myeloma and is the basis for why allografting might have a place in controlling this disease.[90] Patients are generally given myeloablative chemotherapy (as with autografting) followed by matched-sibling or unrelated donor haemopoietic stem cells. Nine studies are summarised in table 4 which shows that treatment-related mortality after full bone-marrow transplant is higher than the 10–15% normally seen for leukaemia, ranging from 10% to 63% (median 41). This high rate reflects the older age and increased infection problems in multiple myeloma patients, who frequently have a severe immune paresis and poor performance status at the time of transplant.[91–100] The European Bone Marrow Transplant registry[100] showed that

	Median age (years)	Proportion with previous autograft (%)	Treatment-related mortality (%)	Proportion attaining complete remission (%)	Overall survival (months [proportion of patients alive at time])	Event-free survival (months [proportion of patients at time])
Study						
Bensinger et al, 2001 (n=136)[91]	45	0	63	34	60 (22%)	60 (14%)
Cavo et al, 1998 (n=19)[92]	43	0	37	34	48 (26%)	48 (21%)
Gahrton et al, 1995 (n=162)[93]	43	..	25	44	48 (32%)	72 (34%)*
Kulkarni et al, 1999 (n=33)[94]	38	36	51	37	36 (39%)	36 (36%)
Mehta, et al 1997 (n=97)[95]	45	68	54	26	36 (27·5%)	36 (12·8%)
Reece et al, 1995 (n=26)[96]	48	4	31	..	36 (47%)	36 (40%)
Marit et al, 1996 (n=137)[97]	..	..	51	51	28§	33·3%*
Björkstrand et al, 1996 (n=189)[98]	..	..	41	48	60 (30%)	60 (20%)
Seiden et al, 1995 (n=21)[99]	43	0	10	33	24 (60%)	24 (33%)
Gahrton et al, 2001[100]						
1983–93 (n=334)	43	..	46	45	24 (45%)	7§
1994–98 (n=223)	44†	..	30	48	24 (65%)	19§
1994–98 (n=133)	46‡	..	35	39	24 (52%)	15§

*Patients in complete remission. †Received bone-marrow rescue. ‡Received peripheral-blood stem cell rescue. §Median value.

Table 4: **Results of allogeneic transplantation in patients with myeloma**

patients who received allotransplant in 1994–98 had a lower treatment-related mortality and better survival than patients treated in 1983–93 (figure 5). This difference was due mainly to enrolment of patients earlier in their disease and to improvements in supportive care, although, despite earlier enrolment, relapse rate did not decrease.

Non-myeloablative allotransplants

However, on balance, full allogeneic bone marrow transplantation has only a very small role in the overall management of myeloma. This limitation has led to the idea that modified bone-marrow transplant could be undertaken, in which cytotoxic treatment given just before stem cells is reduced in intensity but remains sufficient to enable the graft to take and produce the allogeneic antitumour effect.

In a study,[101] consolidation of the response achieved with melphalan 200 mg/m^2 autograft followed by a non-myeloablative sibling allograft conditioned with total body irradiation at 2 Gy was investigated. Of the 54 patients, 16% died of transplant-related complications, and 38% developed acute and 46% chronic graft-versus-host disease. Treatment-related mortality was higher in patients who had non-responsive disease. 57% patients achieved complete remission with 83% overall response.[101] At a median follow-up of 18 months, 78% patients were alive. Overall and event-free survival were better for responding than non-responding patients.

Badros and colleagues[102] treated 31 relapsed or recently diagnosed patients who had high-risk myeloma with non-myeloablative melphalan-based conditioning regimens. At a median follow-up of 6 months, 61% patients had achieved complete or near-complete remission. These studies' findings show the feasibility of undertaking non-myeloablative-allogeneic transplants, but further assessment is needed.

Interferon

Interferons were first isolated from human leucocytes and given as myeloma treatment more than 20 years ago.[103] Interferons have been used for induction and maintenance treatment in myeloma. Meta-analysis of up to 24 randomised trials by two independent groups has been needed to show weak but definite benefit for interferons.[104,105] The median overall survival was prolonged by 4 months in smaller trials. The survival benefit is small and needs to be balanced against cost, toxic effects, and quality of life.[104,105] Pegylated interferon is now available, is less toxic, and opens up the possibility of better compliance at higher doses.[106]

Steroids

In a randomised study, the role of steroids as maintenance treatment was assessed in patients with myeloma who initially responded to VAD-based chemotherapy. No patient received a stem-cell transplant. The study compared 10 mg with 50 mg oral prednisone given on alternate days for remission maintenance in 250 patients. The 50 mg dose significantly improved overall and event-free survival.[107] This finding was not surprising, since all these patients were already responding to dexamethasone before receiving prednisone. Long-term use of steroids maintenance is not an attractive option because of notable side-effects, such as osteoporosis, avascular necrosis of bone, hyperglycaemia, hypertension, infectious complications, weight gain, change in mood, and myopathy.[107]

Monoclonal antibodies/dendritic cells

Other immune manipulations involve the specific use of antibody to terminally differentiated B cells (humanised HM1.24 monoclonal antibody, Chugai, London, UK),[108] antibody to interleukin 6,[109] specific anti-idiotypic antibodies, and targeted dendritic cells are all being tested,[110,111] but show logistic difficulties and indifferent

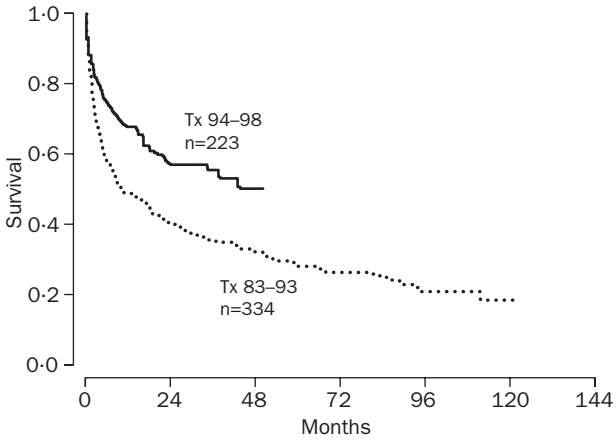

Figure 5: **Overall survival after bone-marrow transplant according to time of allogeneic transplantation**
Adapted from Gahrton G, Svensson H, Cavo M, et al. Progress in allogeneic bone marrow and peripheral blood stem cell transplantation for multiple myeloma: a comparison between transplants performed 1983–93 and 1994–98 at European Group for Blood and Marrow Transplantation centres *Br J Haematol* 2001; **113:** 209–16 (reference 100).

results. However, the mechanisms involved might be exploited at a molecular level in the future.

Bisphosphonates and kyphoplasty

Most new patients with myeloma have detectable bone disease on radiography (local destruction with osteolytic lesions or generalised osteoporosis) at the time of diagnosis, and 70–80% have symptoms from these changes.[112] Despite the efficacy of chemotherapy, most patients with advanced myeloma develop clinical manifestations related to osteolytic bone destruction. With the spine, decompression might be needed and new techniques such as vertebroplasty or kyphoplasty could increasingly be used early. Kyphoplasty is a minimally invasive fracture-reduction technique involving injection of cement (polymethylmethacrylate) into vertebral compression fractures. In a study of 55 consecutive kyphoplasties done in 18 patients, 34% of the height lost due to vertebral fractures was restored, with significant clinical improvement of pain and function.[113]

Data suggest that some bisphosphonates, particularly aminobisphosphonates such as pamidronate and third-generation zoledronic acid, could have direct antitumoural effects, at least in vitro.[114,115] Biphosphonates prevent osteoporosis and in a randomised study, pamidronate increased the survival of myeloma patients on salvage chemotherapy and also reduced skeletal events.[116] All patients with myeloma should receive oral (clodronate or ibandronate) or parenteral (pamidronate or zoledronate) bisphosphonate treatment throughout the course of their treatment and maintenance.

Future research follows the observation that there is overexpression of receptor-activator of NF-κB ligand in patients with myeloma, and it is produced by both the stromal cells and myeloma cells. Oyajobi and colleagues[117] and Shipman and colleagues[118] have used a very effective inhibitor of osteoclast activity, receptor-activator of NF-κB Fc, which is a soluble antagonist to the receptor-activator of NF-κB that resides on osteoclasts and receives the signals that are important for osteoclast formation and activation and thus blocks the effects of stimuli that activate the osteoclast.[117,118] Receptor-activator of NF-κB Fc, a humanised monoclonal antibody (AMG 162) has entered phase I studies. Also, osteoprotegerin construct (AMGN-0007) targeting these pathways has entered clinical trials.[119]

Thalidomide and its analogues

To target the increased microvessel density seen in the bone marrow of patients with active myeloma, thalidomide was assessed in patients with end-stage refractory myeloma based on the work of Vacca and colleagues, showing that thalidomide could induce apoptosis of neovasculature and inhibit angiogenesis in animals.[120] Indeed, bone-marrow microvascular density is increasingly becoming an important prognostic indicator.[121] Thalidomide and its potent immunomodulatory derivatives also directly induce apoptosis or G1 growth arrest, even in drug-resistant myeloma cells. In the host cells, they also abrogate increased secretion of interleukin 6 and VEGF, triggered by binding of myeloma cell to bone-marrow stromal cells, and stimulated autologous natural-killer-cell-mediated antimyeloma immunity.[34,36]

Singhal and colleagues[122] reported on the use of thalidomide alone in the treatment of refractory myeloma. The study design called for a gradual increase in dose to 800 mg daily. Because of toxic effects only 5% of patients received the dose; most patients received 400 mg daily. The follow-up of this study, including 169 patients, shows a response rate of 37% and 2-year survival of 60%. The most common toxic effects (≥grade 3) were sedation or somnolence (25%), constipation (16%), sensory neuropathy (9%), and deep-vein thrombosis (2%).[123]

The logical next step is to use thalidomide in combination and to see whether the addition of thalidomide to dexamethasone or chemotherapy results in higher responses. In studies of thalidomide and dexamethasone responses of 26–48% have been reported, and with chemotherapy 44–86%, in refractory or relapsed myeloma.[124]

These results have prompted the investigation of this combination in new patients. Phase II studies have been started with thalidomide alone and in combination with dexamethasone for induction treatment. In a study of 28 patients who received thalidomide alone, the response rate was 36%, and for those who received thalidomide and dexamethasone it was 72%, with 16% of patients achieving complete remission.[125] Thalidomide is also being used in combination with chemotherapy for induction. A higher rate of thromboembolism (16%) has been reported when thalidomide is used in combination with doxorubicin-containing regimens than in those without doxorubicin.[126]

The optimum dose of thalidomide is still uncertain, although responses have been documented with doses as low as 50–100 mg daily.[124] The role of thalidomide maintenance is currently being addressed in French and UK Medical Research Council randomised trials.

Thalidomide analogues are now available for clinical use and in the phase I dose escalation trial (5–50 mg daily) with oral CC-5013 in 27 relapsed or refractory patients with myeloma, no dose-limiting toxic effects were noted within the first 28 days, but grade 3 myelo-suppression developed after day 28 in all 13 patients receiving 50 mg CC-5013. 25 mg per day was, therefore, the maximum tolerated dose. Of the 24 assessable patients, 17 had 25% decrease in paraprotein, including 29% in partial remission.[127] No patient achieved complete remission. No responses were seen with 5 mg, whereas a third of patients responded to 200–800 mg.thalidomide In the phase II study, of the 83 assessable patients with relapsed or refractory myeloma, the overall response rate was 38% (6% complete remission) with stable disease in 47% of patients.[128] Myelosuppression was the most common side-effect; severe somnolence, constipation, or neuropathy were not seen. A phase III study is continuing. Two other thalidomide analogues, CC-4047 and ENMD-0995 have entered phase I trials.[129,130]

Other new drugs

Proteasome inhibitors inhibit the degradation of ubiquinated proteins, including cell-cycle-regulating proteins such as cyclins and cyclin-dependent kinase inhibitors, which regulate cell-cycle progression.[131] Specifically, bortezomib, a boronic-acid dipeptide with selective activity as a proteasome inhibitor, inhibits activation of NF-κB , blocks up-regulation of interleukin 6 induced in bone-marrow stromal cells by myeloma-cell binding, directly induces apoptosis in myeloma cells resistant to dexamethasone, alkylating agents, and anthracycline, and lowers VEGF concentrations and associated angiogenesis.[34,36] A multicentre phase II study in 202 patients with advanced myeloma (83% had received thalidomide and 64% had received high-dose treatment) showed that the overall response rate was 35% with 4% achieving complete remssion. 6% of the patients who achieved partial remission met all the criteria for

complete remission except negative immunofixation (designated near-complete remission). The median overall survival was 16 months (median 12). Grade 3 adverse events were thrombocytopenia (28%), fatigue (12%), peripheral neuropathy (12%), and neutropenia (11%). Grade 4 events occurred in 14% patients.[132] A phase III study is underway. This drug has received US Food and Drug Administration (FDA) and European Agency for Evaluation of Medicinal Products (EMEA) approval for relapsed myeloma.

Also, drugs such as farnesyl-transferase inhibitors, PI-88, VEGF inhibitor PTK 787/ZK 222584, arsenic trioxide, β lapachone, TNF-related apoptosis-inducing ligand, 2-methoxyoestradiol, histone-deacetylase inhibitors such as suberoylanilide hydroxamic acid are entering clinical trials. Figure 3 shows the extraordinary range of biological targets and the drugs now becoming available for myeloma patients specific for the microenvironment, including bone, stromal cells, vascular endothelium, the transferase pathway, and protein metabolism.[124–141] Although major progress has been made in treating myeloma through the discovery of these new drugs, there is no role at present for these experimental strategies as a replacement for standard treatment, which should be induction therapy followed by stem-cell transplantation for eligible patients.

Support groups

Increasingly, patients are being encouraged to be involved in their treatment decisions and also in service and research delivery. To this end, the International Myeloma Foundation (http://www.myeloma.org) was the first international group to organise worldwide seminars for patients and their families and support sessions, and has an international think tank directing research strategies. The Multiple Myeloma Research Foundation is a similar organisation (http://www.multiplemyeloma.org).

Concluding remarks

For patients who have myeloma, the chances of true cure—ie, eradication of the last myeloma cells—are low, although with autotransplantation, which has a low risk of treatment-related mortality, a substantial proportion of patients survive for more than 10 years. We have described a group of myeloma patients receiving modern treatment who might have disease detectable by molecular methods but have been in long-lasting complete remission for longer than 10 years, lead normal lives, and who are free from symptoms relating to myeloma or its complications.[142] These patients were young (median age 45 years) at diagnosis and had attained complete remission with induction treatment and all had received one autotransplantation.

Additionally, a better understanding of the biology of myeloma means that quite soon we might be able to define and tailor-make at diagnosis which patients will most readily respond to which biological treatments. To suppose that the biological opportunities presenting themselves in myeloma should be the basis of our research for the immediate future seems reasonable. With drugs such as proteasome inhibitors, this research in myeloma, with its good markers of tumour mass, may lead the way for application to other cancers. However, randomised trials looking at advances in treatment might need to be focused not only on changes in median disease-free survival but on increasing the proportion of patients surviving at 10 years with a normal quality of life, because this endpoint could be the way to lead us to true cure.

Conflict of interest statement

R Powles sits on advisory boards and has received honoraria and research grants from Pfizer, Janssen-Cilag, Merck-Sharpe and Dohme, Chugai, Novartis, Millennium, Ortho Biotech and Vicuron, all of which manufacture drugs used to treat myeloma or its complications. He is also a consultant to BioPartners, a biopharmaceutical company, which does not and is not likely to promote any of its products for multiple myeloma. B Sirohi sits on advisory boards and has received honoraria from Pfizer and InterMune, which manufactures drugs used to treat myeloma or its complications.

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