Multiple Myeloma: Pathogenesis and Treatments

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CLINICAL POINTS

Multiple myeloma is a haematological malignancy caused by a clonal B cell proliferation that produces terminally differentiated plasma cells.

The main presenting symptoms of multiple myeloma include bone pain, fatigue and recurrent infection.

The main clinical findings in multiple myeloma include hypercalcaemia, renal insufficiency, anaemia and bone lesions.

The International Staging System (ISS) uses serum beta2-microglobulin (Sβ2M) and serum albumin levels to stage the illness.

Treatments include conventional chemotherapeutic regimes, thalidomide and its analogues, proteasome inhibition therapies (e.g. bortezomib), anti-oestrogenic therapies, stem cell transplantation and treatment of complications like bone disease.

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Abstract

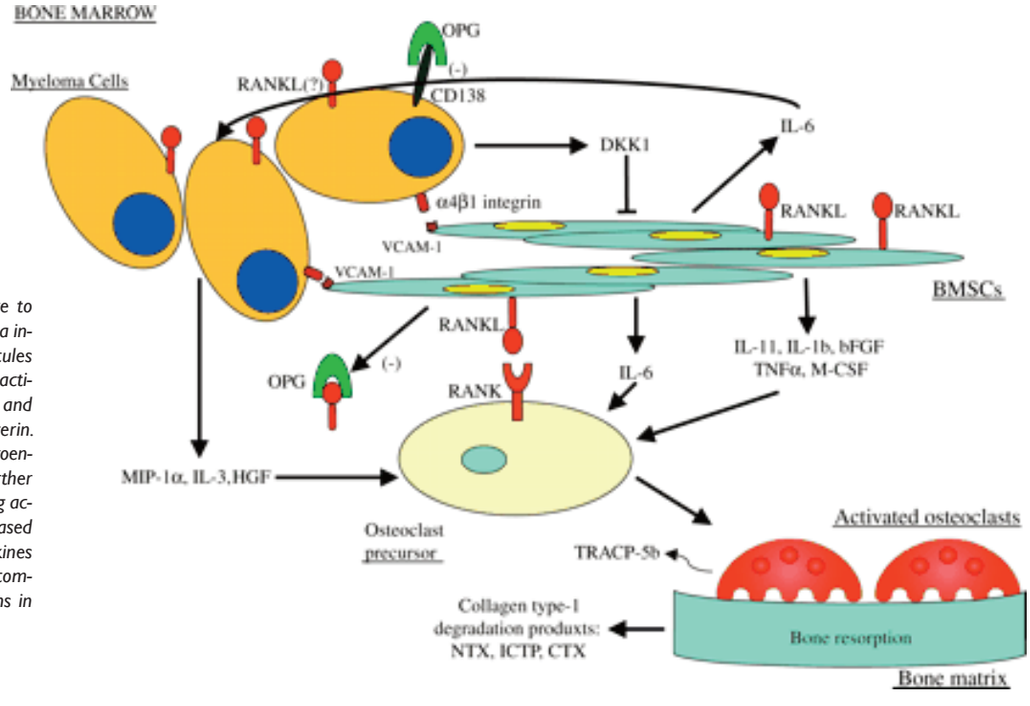
Multiple myeloma is a clonal B cell malignancy involving terminally differentiated plasma cells. It causes nearly 1% of cancer deaths worldwide. Failure of apoptosis, angiogenesis and bone marrow interaction with malignant cells all contribute to the pathogenesis of the disease. Bone disease remains one of the most serious aspects of Multiple Myeloma. Diagnosis involves measurements of abnormal cells and protein in the serum, protein in urine or lesions and end organ damage, in addition to the detection of tumours. Serum β2-microglobulin and serum albumin are important in determining prognosis, which is generally poor. Current treatments include steroids, alkylating agents, antimetabolic agents and other cytotoxic drugs. However, research is ongoing into other agents including proteasome inhibitors, thalidomide and its analogues, and anti-oestrogenic treatments. Stem cell transplantation is another important aspect of treatment. Treatment of bone pain is an important aspect of management also, utilising bisphosphonates, analgaesics, radiation therapy and surgical intervention. Newly identified molecular markers of disease are the subject of exciting research that aims to identify new therapeutic regimes.

Introduction

Multiple myeloma (MM) is an important haematological malignancy, mainly affecting middle aged and elderly populations[1,2,3]. Multiple myeloma caused 137 (1.7%) of 7870 cancer deaths in 2004 in Ireland[4], and causes approximately 0.9% of all cancer deaths worldwide[5]. 85,704 new cases were diagnosed in 2002, indicating the huge international burden of this illness[5]. Given the great burden of MM, much work has been done in attempting to elucidate the molecular mechanisms behind it, with an aim of controlling symptoms and improving overall survival. This review is intended to give a brief overview of the pathogenesis, existing treatments and emerging therapies of this important haematological malignancy.

Pathogenesis

Multiple myeloma (MM) is a clonal B cell malignancy involving terminally differentiated plasma cells[1,2,3]. This means that there is a proliferation of plasma cells expressing one particular type of immunoglobulin i.e. one clone of plasma cells. Rather than producing normal antibodies, as occurs with normal plasma cells, monoclonal plasma cells produce a monoclonal protein (M-protein). These M-proteins have structures similar to normal antibodies (immunoglobulins), and are made up of light and heavy chains. →



→ ***Fig. 1.*** *Myeloma cells adhere to bone marrow stem cells (BMSC) via interactions of cell surface molecules causing production of osteoclast-activating factors including RANKL and downregluation of osteoprotegerin. Modification of bone marrow microenvironment by cytokines causes further expression of RANKL. The resulting activation of osteoclasts causes increased bone resorption. Many other cytokines are involved, indicating the very complex nature of cell-cell interactions in this disease.*

Several processes are central to the pathogenesis of MM. The main pathological feature is unregulated proliferation of a single clone of plasma cells, known as myeloma cells. This proliferation is mainly due to failure of the cells to die by apoptosis, as would happen in the normal cell cycle.

In a normally functioning immune system, rearrangement of DNA occurs within cells to produce the various types of antibodies used in day-to-day defence against pathogens. This flexibility of DNA regulation allows for malignant change of plasma cells, resulting in uncontrolled proliferation. The malignant plasma cells can build up in the bone marrow, forming masses or tumours. An increase in bone marrow angiogenesis occurs also, ensuring the growing tumour has an adequate blood supply. These masses contribute to some of the complications and clinical features of MM (see Table 2), such as tumour-induced bone destruction[3]. Indeed, bone disease is one of the most important aspects of MM, thus its pathogenesis is also described below.

Failure of apoptosis

One of the main pathological processes of MM is failure of apoptosis of one clone of myeloma cells, resulting in their uncontrolled proliferation[7]. In vitro studies have shown that the majority of MM cells require activation of EGF (epidermal growth factor) surface receptors for survival. It has conversely been shown that inhibitors of EGF receptors can induce apoptosis in MM cells[8]. These receptors bind heparan-sulphate proteoglycans (HSPGs), thereby implicating HSPGs in the failure of apoptosis also [8].

Angiogenesis

The bone marrow of an MM patient displays increased angiogenesis, the degree ofwhich corresponds to extent of disease. The new blood vessels bring oxygen and nutrients to the developing tumour, aiding its growth. Rajkumar et al. (2002) have demonstrated an increase in bone marrowangiogenesis present in MM by comparing the Median Microvessel Density (MVD) in bone marrow samples from MM patients to those from healthy controls[9]. The new tumour vessels are different from the normal vasculature, being thinner and more tortuous. They display increased endothelial cell turnover in the vessel lining, secreting growth factors that stimulate myeloma cells within the bone marrow[10,11]. Patients have been demonstrated to have increased rates of expression of cytokines that promote angiogenesis, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), insulin-like growth-factor-1 (IGF1) and interlukin-6 (IL-6)[10,11].

▼ ***Table 1.***
Diagnostic criteria for multiple myeloma.

Minimal diagnostic criteria for multiple myeloma[15,27]

1. 1 of: Presence of ≥10% abnormal plasma cells in the bone marrow .
   Histological proof of presence of a plasmacytoma (mass of myeloma cells).
2. Features of end organ damage:
   hypercalcaemia; renal insufficiency; anaemia; and bone lesions.
3. 1 of: Serum M protein ≥3g/dL.
   M protein in the urine and osteolytic.

Bone marrow interaction of myeloma cells

The inflammatory mediator TNF-α, present in high quantities in MM patients, activates a transcription factor called NFκB in both MM cells and normal bone marrow cells. NFκB upregulates the production of a cytokine called IL-6[6]. IL-6 allows MM cells attach to stromal cells in the bone marrow. This attachment results in a series of interactions that allow progression of disease, e.g. by preventing apoptosis of MM cells and by increasing angiogenesis.

Bone disease

MM triggers osteolysis (breakdown of bone) without reciprocal activation of osteoblasts (cells that produce bone). This differs from the bone disease seen in other malignancies, where osteolysis occurs but is accompanied by osteoblast activation[12].

MM cells activate osteoclasts (cells that break down bone) by increasing expression of RANKL (receptor activator of nuclear factor κB ligand) and by decreasing expression of its inhibitor, osteoprotegerin (see Fig. 1). This mechanism is evidenced by the ability of RANKL antagonists to prevent osteolysis and tumour progression in in-vitro MM models[12]. A number of other osteoclast-activating factors (OAFs) such as IL-1, TNF-α, macrophage inflammatory protein-1α (MIP-1α) and MIP-1β, also contribute to the stimulation of osteoclasts[12,13].

Several studies have also suggested a role for Wnt antagonists in the bone destruction seen in MM[12-14]. Wnt regulates the differentiation of mesenchymal precursors into chondroblasts or osteoblasts. Blockage of Wnt signalling, as appears to occur in MM, results in an abundance of chondroblasts with few or no osteoblasts[12]. However, the role of Wnt in bone formation and destruction remains to be fully elucidated.

Diagnosis and staging

The minimal diagnostic criteria for MM are outlined in Table 1.

Some patients that do not have a detectable serum M protein but meet all of the other diagnostic criteria are considered to have nonsecretory myeloma[15]. Patients presenting with nonsecretory myeloma are approximately ten years younger than those with typical MM. Hypercalcaemia, anaemia and renal failure are less common than in typical MM but survival and treatment options are similar[28].

Measurement of the serum ratio of κ to λ free light chains is also important in measuring disease burden, disease progression and therapeutic response in MM. Monoclonal disorders of plasma cells are the only disorders to exhibit derangement of the serum free light chain ratio[29].

Under the International Staging System 2005, the most powerful predictors of survival in MM include serum levels of beta2-microglobulin (Sβ2M), albumin and creatinine, platelet count and age[30]. However, there have been suggestions that the absence of tumour-related biological factors, like molecular markers, may limit the use of ISS staging in the future[29].

Patients with a serum Sβ2M less than 3.5mg/L and serum albumin greater than 3.5g/dL generally have a better prognosis (median survival of 62 months) compared to ➔

Complication	Freq.	Presentation	Cause
Anaemia[21]	85.3%	Tiredness, pallor, breathlessness on exertion	Depression of erythropoiesis
Pathological fracture[19,20]	60%	Bone pain	Osteolysis
Renal impairment[16,22,23]	50%	Hypercalcaemia, raised creatinine	Blockage of tubules by circulating myeloma cell proteins
Hypercalcaemia[2]	33%	Confusion, depression, nausea, vomiting, constipation, renal stones, arrhythmias	Bone resorption; renal impairment
Thrombosis[26]	30%	Dependent on clot location	Decreased protein S levels causing prothrombotic state
Amyloidosis[22,25]	5-10%	Fatigue, shortness of breath, weakness, paraesthesia	Aggregation of misfolded immunoglobulin light chains, similar to those produced by myeloma cells
Spinal cord compression[15-18]	5%	Pain (localised to dermatome), motor weakness, loss of sensation, incontinence	Vertebral compression fractures
Hyperviscosity[22,24]	4.2%	Neurological symptoms, visual impairment, cryoglobulinaemia, haemorrhage	Increased myeloma protein levels in circulation

▲ ***Table 2.***
Presentations and complications of multiple myeloma.

those with higher Sβ2M and lower albumin (median survival 44 months)[30]. However, treatment improvements outlined below have greatly improved prognosis and increased survival times beyond those described by this system.

Prognostic factors in MM are numerous and relate to a number of different aspects of the disease. They include the diagnostic criteria outlined above, as well as other factors such as bone marrow microvessel density, LDH, CRP, age and response to treatment[29].

Pharmacological treatment

Cytotoxic drugs

Current management of MM involves a number of different cytotoxic drug regimes, in addition to Stem Cell Transplantation (see below). The choice of regime is dependent on many factors including the age of the patient and severity of the disease. A variety of cytotoxic drugs are commonly used (see Table 3). Regimes used in initial stages of treatment include:

VAD (vincristine, doxorubicin and dexamethasone)

VAMP (vincristine, doxorubicin, methotrexate and prednisone)

C-VAMP (cyclophosphamide, vincristine, doxorubicin, methotrexate and prednisone)

IDEX (idarubicin and dexamethasone)[31, 32]

In cases of MM not eligible for transplant, patients may receive any of three regimes including MPT (melphalan, prednisone, thalidomide), MPV (melphalan, prednisone, bortezomib) and RV (lenalidomide, bortezomib) plus dexamethasone[33].

Side effects common to all cytotoxic drugs include nausea, vomiting, oral mucositis, tumour lysis syndrome (hyperkalaemia, hyperphosphataemia, hyperuricaemia, hypocalcaemia, renal damage, and arrhythmia), bone marrow suppression, alopecia and teratogenicity[34]. There are also additional side effects associated with each individual drug.

Proteasome inhibiting drugs (Bortezomib)

Bortezomib has a high affinity for the catalytic site of a proteasome that regulates intracellular protein turnover by degrading ubiquitin-tagged proteins[5].

Part of bortezomib's mechanism of action involves blocking the activation of NFκB (involved in bone marrow interaction). However, this mechanism alone is not sufficient to explain the full effects of the drug[5]. It is also thought to prevent myeloma cell proliferation by downregulating genes that code for growth factors. Additionally, bortezomib can induce apoptosis[5]. Some reports suggest that the drug's capacity to inhibit DNA repair may reduce tumour resistance to steroids and conventional cytotoxic agents[35-37].

Common side effects of bortezomib include asthenia, thrombocytopaenia, peripheral neuropathy and postural hypotension[37]. A 27% response rate (complete or partial) to bortezomib has been suggested. Reasons for lower response to bortezomib include age of ≥65 years and ≥50% bone marrow plasma cell infiltration[38].

Thalidomide and its analogues

Thalidomide analogues, such as lenalidomide, revlimid and actimid, have been found to be effective in the treatment of MM[39]. They are believed to act by firstly, decreasing levels of TNF-α (the inflammatory mediator involved in bone marrow interaction of myeloma cells) and secondly, increasing cytotoxic abilities of both T lymphocytes and Natural Killer (NK) cells (helping to create a more vigilant immune system to target malignant cells)[5,39].

Thalidomide-based drugs may also disrupt MM cell-bone marrow interaction by changing density of cell surface receptor molecules[5,39], in addition to stimulating erythropoiesis, helping to counter the anaemia of MM[39,40]. There are also suggestions that thalidomide may also decrease angiogenesis in MM since animal studies show that thalidomide inhibits the angiogenesis-inducing cytokine bFGF. However, it has since been reported that thalidomide did not have a major effect on microvessel density in actual MM patients[5].

A response rate of 32% in heavily pre-treated patients has been suggested[32]. The main side effects of this therapy include constipation, rash, peripheral oedema, sedation, tremor, fatigue, thrombocytopaenia, neutropaenia and thromboembolic events[41-43].

Anti-oestrogenic treatments

Emerging research is showing that anti-oestrogenic treatment is a promising area for clinical research in multiple myeloma. Both normal and cancerous plasma cells express oestrogen receptor mRNA and protein[44]. High concentrations of anti-oestrogens arrest MM cell division[44]. This may be helpful in preventing uncontrolled proliferation which, as mentioned above, is integral to the pathogenesis of MM. Lower concentrations of anti-oestrogens trigger MM cell apoptosis[44]. ➔

Drug	Class	Main mechanism of action
Vincristine	Vinca alkaloid	Inhibits cell division, preventing myeloma cell proliferation
Doxorubicin	Anthracycline antibiotic	Inhibits cell division, preventing myeloma cell proliferation
Idarubicin	Oral anthracycline	Inhibits cell division, preventing myeloma cell proliferation
Dexamethasone	Synthetic adrenal corticosteroid	Interferes with NF-κB activation; interferes with apoptotic pathways
Methotrexate	Antimetabolite and antifolate agent	Inhibits DNA/RNA synthesis, preventing myeloma cell proliferation
Prednisone	Synthetic glucocorticoid	Alters gene expression; induces cell differentiation; stimulates apoptosis in sensitive tumour cell populations
Cyclophosphamide	Alkylating agent	Inhibits DNA replication, preventing myeloma cell proliferation
Melphalan	Alkylating agent	Inhibits DNA replication, preventing myeloma cell proliferation

▲ ***Table 3.***
Current treatments for multiple myeloma[34,35].

Studies have shown that these anti-proliferative and pro-apoptotic properties do not have an effect on normal B cells and may affect MM cells that are resistant to first-line treatments[5,45]. This is an emerging area of research and more studies are needed to determine the usefulness of these therapies.

Stem cell transplantation

Stem cell transplantation (SCT) aims to wipe out the malignant cells and replace them with stem cells. These stem cells have the ability to differentiate and replicate, replacing the malignant cells with normally functioning cells (see Fig. 2).

Conditioning regimens are carried out in advance to destroy cancer cells, and to suppress the immune system adequately to prevent rejection of the new cells. The regimens can be divided into three groups.

a. Myeloablative conditioning (MAC) destroys all remaining cancer cells and cause immunosupression to allow an allogeneic transplant.

b. Non-myeloablative conditioning destroys cancer cells but does not cause full immunosupression.

c. Reduced intensity conditioning (RIC) lies between (a) and (b) in terms of intensity. The aim is to achieve adequate immunosupression but to minimise toxicity[46].

MAC is associated with higher non-relapse mortality than RIC, possibly due to the highly toxic nature of the conditioning procedure. However, RIC is associated with a lower response rate and higher rates of relapse/progression[47].
There are two types of SCT that have been used in MM. Autologous transplants use stem cells come from the patient themselves, while allogeneic transplants use donor cells from another individual[46]. Allogeneic SCT is a very toxic procedure with a high mortality rate, mainly due to infection and GVHD (graft-versus-host disease). It is now rarely used as part of MM treatment.

Peripheral blood stem cell transplantation (PBSC) following reduced-intensity conditioning (RIC) uses peripheral stem cells rather than bone marrow stem cells for SCT. The cells are mobilised using chemotherapy with agents including cyclophosphamide and G-CSF (granulocyte-colony stimulating factor)[32]. A large study conducted on data from 1994 to 2003 concluded that both positive (e.g. progression-free survival) and negative (e.g. relapse rate) outcomes of PBSC transplantation are similar to those found in bone marrow transplantation[47]. PBSC is now widely used for autologous transplant in MM treatment[32].

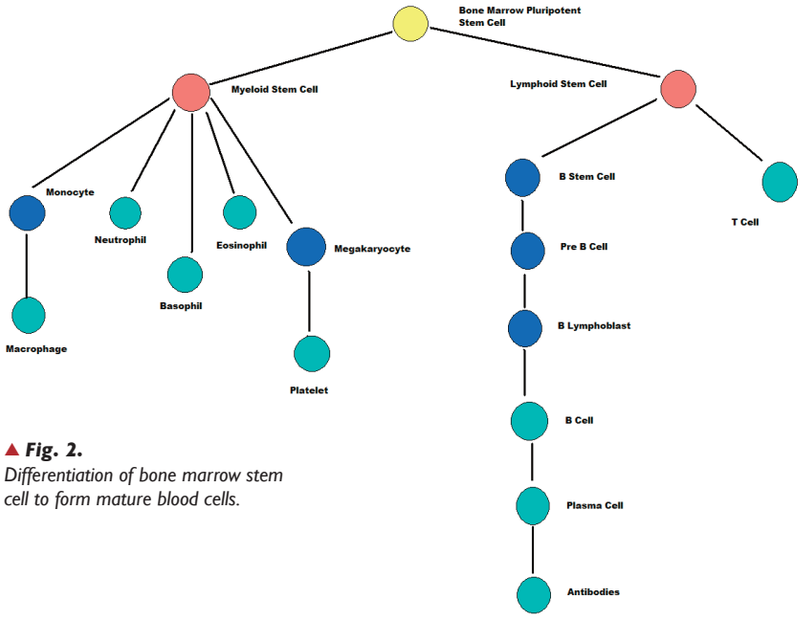
The current standard of care for MM in patients under sixty-five is high-dose treatment with autologous SCT. It is also suggested that response to induction therapy is not a valid predictor of response to autologous SCT, and autologous SCT should be considered in all younger MM patients, even those with a poor response to induction therapy[32].
An Irish study in St. James's Hospital reported five-year progression free survival and overall survival rates of 13% and 55% respectively, following corticosteroid-anthracycline treatment and autologous SCT[32]. Factors associated with a poorer outcome in SCT include low albumin, high Sβ2M, high CRP and high LDH, and the primary side effects are infection and graft-versus-host-disease[48,49].

Treatment of bone involvement

There are four main dimensions to the treatment of bone disease in MM: bisphosphonates, analgesia, radiation therapy and surgical procedures[12]. Bisphosphonates inhibit production and induce apoptosis of osteoclasts, preventing bone resorption[50]. Regularly used drugs include pamidronate and zoledronic acid[51]. Radiation therapy in MM bone disease is generally reserved for painful lesions, as are analgaesics, although radiation therapy has also been shown to prevent further vertebral fractures in MM patients[52]. Surgical interventions such as percutaneous vertebroplasty (involving the injection of cement into the vertebral body) have been used in the management of spinal fractures in MM-related bone disease with some excellent results[12].
More recently, there have been reports of proteasome inhibitors (see above) being used as a therapy for MM-related bone disease. They are thought to inhibit osteoclasts and bone resorption as well as stimulating osteoblast differentiation[52].

Conclusion

Given its bleak prognosis and its high incidence, Multiple Myeloma is a disease that has inspired much interest in mechanisms of pathogenesis and possibilities for treatment. Today, it remains an incurable illness. However, great strides have been made in increasing our knowledge of this fatal disease and discoveries have led to the development of new and improved therapies. Multiple Myeloma is now becoming a somewhat chronic illness with patients who respond well to treatment living well beyond the survival times outlined in the International Staging System. Research is ongoing, with a myriad of new pathological and prognostic molecular markers being discovered. New therapeutic techniques are being developed also, aiming to increase quality and duration of survival. It now remains to be seen what impact this research will ultimately have in the fight against Multiple Myeloma. ■



▲ ***Fig. 2.***
Differentiation of bone marrow stem cell to form mature blood cells.

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