

Multiple Myeloma

An update on disease biology and therapy

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Abstract

Multiple myeloma is a malignancy of immunoglobulin producing plasma cells. Clinical features include bone pain due to lytic bone lesions or pathological fractures, anemia, symptomatic hypercalcemia, renal insufficiency, recurrent infections and amyloidosis. In the last few years, there have been considerable advances in the understanding of the biology of this disease. While multiple myeloma is biologically diverse, several oncogenes are activated in this illness. In addition, the role of the bone marrow microenvironment to support the growth and survival of the malignant cells has been well described. In this review, we discuss recent developments in the molecular pathogenesis of myeloma. These recent observations are being translated into novel therapeutic approaches that target both the tumor cell as well as the stroma. Current therapeutic strategies are discussed.

Introduction

Multiple myeloma is a hematological malignancy of terminally differentiated plasma cells. Plasma cells develop from B cells and produce antibodies in response to offending antigenic stimulation. In most patients, the disease is restricted to sites of active hematopoiesis within the axial skeleton, skull, ribs and proximal regions of the long bones.¹ The American Cancer Society estimates that 14,600 new patients will be diagnosed with myeloma and 10,900 will die in 2003 due to the disease in the United States.² The disease is more common in males and its incidence is twofold higher in African Americans compared to Caucasians.³ In 90% of patients, the plasma cells secrete a monoclonal immunoglobulin (IgG 60%, IgA 10%, free light chains 20%) with the remaining 10% of patients having non-secretory myeloma.

Patients with multiple myeloma usually present with symptoms related to the presence of lytic bone lesions, anemia, renal failure and immunosuppression. Diagnosis is based on

the presence of a triad of monoclonal immunoglobulin spike in serum and/or urine, lytic bone lesions and bone marrow plasmacytosis (>10%).⁴ A condition known as monoclonal gammopathy of undetermined significance (MGUS) is relatively common in patients older than 50 years (1-2%). While these patients do not have myeloma and therefore do not require therapy, they have an increased risk of developing myeloma and require life-long follow-up.⁵

Etiology

Like most other tumors, the etiology of multiple myeloma is unclear. Both environmental and genetic factors may have important roles in its pathogenesis. Clustering of the disease within families has been observed suggesting a genetic predisposition.^{6,7} The only environmental agents that are clearly linked with myeloma are cigarette smoking, benzene and radiation.^{8,9} Repeated or chronic antigen stimulation due to recurrent or chronic infections and autoimmune disease has been proposed as a possible risk factor. However, a large and comprehensive study that included both Caucasians as well as African Americans did not find any evidence for such an association.¹⁰ The potential link between myeloma and human herpes virus type 8 (HHV-8) has been debated for some time.¹¹ While there is strong evidence for a causal association between HHV-8, Castleman's disease and primary effusion lymphoma, a causal relation with myeloma has not been demonstrated.¹²

Multiple myeloma is similar to other tumors in that the fundamental problem is a genetic one. Using fluorescent *in situ* hybridization (FISH) it is possible to document complex chromosomal abnormalities in more than 50% of patients. With more sensitive techniques, chromosomal abnormalities are identified in almost 100% of patients.¹³ Karyotypic abnormalities are non-random but different among myeloma patients. There is also considerable heterogeneity within the same tumor emphasizing the role of genetic instability in this disease. Complex karyotypic abnormalities are the rule and complexity increases with disease progression.^{3,11} Primary translocations occur early in the disease and are sometimes seen in MGUS while secondary translocations are involved with progression.¹⁴

Primary translocations are simple, reciprocal translocations that juxtapose an oncogene next to one of the immunoglobulin (Ig) enhancers. These genetic errors occur either during IgH class switching, during somatic hypermutation within germinal centers or at the time of V(D)J recombination. Activated

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oncogenes include the *cyclins D1, D2* and *D3*, fibroblast growth factor receptor 3 (*FGFR3*), *MMSET*, *c-MAF* and *MAFB*.^{15,16-18} Secondary translocations usually involve *c-MYC* and are associated with enhanced cellular proliferation.³ In contrast to most other tumors, *p53* and *Rb* are not usually mutated in patients with multiple myeloma.^{19, 20}

The bone marrow stroma plays a critical role in supporting the growth of the myeloma cells by supplying the supporting matrix and production of growth and survival cytokines such as IL-6 and insulin like growth factor 1 (IGF-1).^{21,22} In turn, the myeloma cells produce cytokines that can activate the surrounding stroma (VEGF, IL-6) and osteoclasts (MIP-1 α , IL-1 β).²³ VEGF is a growth and survival factor for myeloma cells and stimulates marrow angiogenesis.²⁴ Osteoclast activation is responsible for the bone resorption and lytic lesions that are found in around 75% of patients with the disease.²⁵

Since the vast majority of patients with myeloma have a detectable monoclonal protein, tumor cell kinetics has been very well studied. Durie and Salmon measured the rate of paraprotein synthesis by malignant plasma cells and thus determined the tumor burden in patients with the disease.²⁶ Tumor burden is the determining factor that guides decisions on when and whom to treat.^{1,27} It is estimated that a patient with advanced myeloma has approximately 10¹² malignant cells or about a kilogram of disease.

Pathologically, the atypical, malignant plasma cells proliferate and infiltrate the marrow in three different patterns – either as multiple plasmacytomas of variable size, diffuse marrow infiltration or a combination of the two.^{28, 29} Diffuse marrow infiltration leads to significant osteoporosis due to osteoclast activation while plasmacytomas activate bone resorption locally leading to the formation of the typical lytic bone lesions seen on routine skeletal surveys.

Patients with multiple myeloma are susceptible to recurrent infections with gram-positive and gram-negative bacteria. Often, they also fail to mount adequate immune responses to vaccinations. These observations suggest that patients with myeloma have profound defects in their immune system.³⁰ The disease is associated with reduced levels of circulating normal immunoglobulins due to both decreased synthesis and enhanced catabolism. This antibody deficiency gets progressively worse with advancing disease and independent of therapy. The mechanisms behind the immunosuppression are not completely understood.^{31, 32}

Clinical Features, Staging and Prognosis

Clinical symptoms and signs occur either due to tumor mass effects or cytokine/protein production by the tumor. Regional tumor growth can cause compression neuropathies of the spinal cord or peripheral nerves. Bone pain occurs due to vertebral compression fractures at sites of osteopenia or lytic bone lesions with the risk of pathological fractures. Patients are prone to recurrent bacterial infections due to defects in the humoral arm

of the immune system (see above). Immunoglobulin light chains can damage the kidneys in many ways. Deposition in the lumen of the renal tubules leads to cast nephropathy while deposition in the mesangium can lead to nephrotic syndrome and progressive renal failure. Light chains are toxic to tubular cells leading to renal tubular acidosis. In 15% of patients, light chains are deposited in other tissues with the potential for cardiac, renal and neurologic (polyneuropathy, autonomic neuropathy) complications, a condition known as amyloidosis. The presence of high concentrations of paraprotein in the blood may elevate plasma viscosity enough to induce symptoms (hyperviscosity syndrome). This is more often seen with IgA myeloma due to the tendency of IgA to form polymers.

The malignant clone of cells suppresses normal erythropoiesis in the bone marrow leading to anemia that is often symptomatic. Postulated mechanisms underlying the anemia are not completely understood but include lack of erythropoietin (EPO) due to any associated renal dysfunction, production of suppressive cytokines, and bleeding.

Bleeding and thrombotic symptoms are uncommon presenting features of the disease. They are thought to be due to amyloid deposition in blood vessels, acquired deficiency in pro-coagulant factors such as Factor X or anticoagulant proteins such as Protein C.

When myeloma is suspected, a diagnostic work-up to confirm or rule out the disease is necessary. At a minimum, complete blood count, blood smear examination, serum calcium and creatinine, serum and urine special protein electrophoresis, bone marrow aspirate and biopsy as well as radiographic examination of the axial skeleton should be performed. Additional studies such as circulating plasma cells, labeling index, flow cytometry, chromosomal studies, β_2 -microglobulin, lactate dehydrogenase and C-reactive protein assist in prognostication.^{33, 34} The disease can only be diagnosed if established criteria are present, and care must be taken not to misdiagnose MGUS as active myeloma.⁴ The role of magnetic resonance imaging as well as positron emission tomography in the initial evaluation of the disease is not clear at present.^{29, 35}

Biologically, myeloma is a very heterogeneous tumor and the course of the disease varies considerably among patients. The median survival is 3 years, but patients may survive from less than 1 year to more than 10 years from diagnosis. Prognosis depends on the disease burden, and only patients with symptomatic disease require therapy. Thus, a staging system has been developed that categorizes patients into 3 stages that correlate well with disease burden, and determine the need for therapy.^{26, 36} The two most important prognostic factors at the time of diagnosis are the serum levels of β_2 -microglobulin and albumin. Additional prognostic factors include C-reactive protein, high levels of circulating plasma cell, elevated plasma cell labeling index, monosomy or deletion of chromosome 13, bone marrow micro vessel density and elevated serum syndecan-1 levels.^{33, 34}

Current therapy for multiple myeloma

At the Mayo Clinic, patients with plasma cell disorders are classified into 4 categories: MGUS, smoldering multiple myeloma (sMM), indolent multiple myeloma (IMM) and symptomatic multiple myeloma (SMM).³⁷ Not all patients with myeloma require therapy; SMM must be distinguished from MGUS and indolent/smoldering myeloma. Patients should only be treated if they have symptoms or active disease. Patients with SMM usually are in Durie-Salmon Stage II or III (defined by any of the following: hemoglobin < 10g/dl, serum IgG > 5g/dl, serum IgA > 3g/dl, elevated serum calcium, urine monoclonal protein excretion > 4g/24 hours, or the presence of lytic bone lesions) and require immediate therapy. The therapeutic armamentarium available to treat myeloma has been steadily increasing.

Pharmacotherapy

Once a decision to treat has been taken, the major determinant of therapy is whether the patient is a candidate for high dose chemotherapy with autologous peripheral blood stem cell transplant (PBSCT) since survival is improved with this approach.³⁸ Patients who are eligible for PBSCT should not be given alkylator therapy because these drugs damage bone marrow progenitor cells and compromise stem cell harvest. Patients who are not eligible for PBSCT should be treated with standard therapy. For many years, the mainstay of therapy has been alkylating agents such as melphalan or cyclophosphamide combined with glucocorticosteroids giving response rates of 50%. However less than 10% of patients achieve a complete response, and the median survival is 3 years. Responses are classified as complete, partial, stable or progression based on the results of serum M protein, symptoms and bone marrow plasmacytosis. More complex chemotherapy regimens lead to higher response rates but survival is not improved.^{1, 27}

Patients who will undergo PBSCT are usually treated with 3 or 4 cycles of combination chemotherapy such as vincristine, doxorubicin and dexamethasone (VAD). However, dexamethasone by itself may be as effective and better tolerated. Relatively healthy patients are often treated with dexamethasone 40mg per day from days 1 to 4, 9 to 12, 17 to 20 with an 8-day treatment free period. Therapy is repeated every 28 days. Autologous stem cells are harvested after high dose cyclophosphamide and G-CSF. Patients are then treated with high dose melphalan (200mg/m²) in an attempt to ablate the malignant clone followed by the infusion of the autologous stem cells to reconstitute normal hemopoiesis. This approach is associated with response rates of up to 90% and an improved survival but is not curative. The survival curves do not plateau and patients continue to relapse and often die of their disease.³⁸ The role of back-to-back "tandem" transplants has been debated for some time. The procedures seem to be relatively well tolerated in select patients and are associated with an acceptable mortality rate (~3%) leading to higher response rates and

improved survival.³⁹ Recently, the French Myeloma Group has reported their experience with tandem autologous transplants for myeloma. While this study clearly demonstrates a superior outcome following tandem transplants, it appears that patients who have a complete or very good partial response within 3 months of their first transplant have a good outcome and can be safely observed. A second transplant is possible if they progress assuming that enough stem cells were collected in the first harvest.⁴⁰

Autologous stem cell harvests are invariably contaminated with malignant plasma cells and contribute to relapse of the disease.^{41, 42} Purgings of the harvested cells does not lead to improved outcomes implying that high dose therapy is not eradicating the malignant clone.⁴³ In an attempt to eliminate stem cell contamination and stimulate a graft versus myeloma effect, allogeneic bone marrow transplantation (BMT) has been performed in eligible patients. The procedure can lead to prolonged disease free survival in a select group of patients but is associated with a 30% mortality and significant graft versus host disease in the survivors.⁴⁴ Thus, allogeneic BMT is considered experimental therapy and patients are treated in the context of clinical trials.

Patients with lytic bone lesions are now routinely treated with bisphosphonates (pamidronate or zoledronic acid) to prevent or delay progression of skeletal complications.⁴⁵ While interferon is often advocated for therapy of myeloma, it is not often used in the United States, and its efficacy is very limited.⁴⁶

Although the disease is often responsive to first line therapy, it invariably progresses and patients require further therapy. Thalidomide has proven efficacy against the disease even among heavily pretreated patients and in general is well tolerated.⁴⁷ The drug interferes with myeloma cells and the surrounding stroma through a variety of mechanisms.⁴⁸ It is usually started at 100mg daily given at bedtime and increased as tolerated. Most patients respond to a dose of 200 – 300mg per day. Due to its well-known teratogenicity, patients must be educated on its use, undergo regular phone surveys, and every prescription requires authorization. Common side effects include somnolence, constipation, peripheral neuropathy, rashes and deep vein thrombosis especially when combined with dexamethasone. The drug is now being used for initial control of the disease and does not compromise responses to high dose chemotherapy and PBSCT or stem cell collection.⁴⁹

Recently, the Food and Drug Administration approved bortezomib (Velcade®) for patients with refractory disease. Bortezomib is a proteasome inhibitor, preventing the normal function of this enzyme complex in degrading cellular proteins that are involved in regulation of the cell cycle.⁵⁰ Up to a third of patients are expected to have a response with a median duration of 12 months.⁵¹ Additional drugs based on thalidomide (IMiDs), NF-κB inhibitors (PS-1145), arsenic trioxide and 2-methoxyestradiol are undergoing clinical trials in patients with the disease.^{48, 50, 52}

Radiation Therapy

Plasma cells are very sensitive to radiation although the mechanisms underlying their sensitivity to this therapeutic modality are not clear. External beam radiation has been used for many years to treat localized plasmacytomas with excellent local control.⁵³ Local radiation therapy is used in patients with myeloma to control pain from lytic bone lesions, symptomatic soft tissue masses and to treat spinal cord compression.⁵⁴ Thus, there has been considerable interest in the use of total body irradiation (TBI) as part of the conditioning regimen prior to stem cell transplantation. The largest study to date has been performed by the French Myeloma Group (IFM) and they showed that combining TBI with high dose melphalan is not superior to high dose melphalan alone; the combined regimen is associated with higher toxicity.⁵⁵ Thus TBI has gone out of favor for conditioning and radiation therapy is used only for palliative control.

Experimental therapy for myeloma

The poor prognosis of patients with myeloma has prompted the exploration of new therapeutic approaches for the disease. Progress in the fields of immunology, tumor biology and virology over the past few years has paved the way for considerable advances in the future. Since myeloma cells express a single type of antibody, this might appear as the perfect tumor specific antigen. Thus there is considerable interest in immunotherapy for the disease using expression of co-stimulatory molecules, generation of tumor cell specific T-cell responses as well as antibody based therapy such as Rituximab (Rituxan®).⁵⁶⁻⁵⁸ Recently, myeloma cells were shown to express high levels of CD52.⁵⁹ Thus, the disease might respond to alemtuzumab, Campath 1H (a monoclonal antibody directed against CD52) and clinical trials are about to start.

In the last few years there has also been considerable interest in the use of gene therapy for this disease. Therapeutic approaches have included the expression of co-stimulatory molecules, secretion of immune activating cytokines and expression of suicide genes in combination with their respective substrates.⁶⁰ Recent work has led to the development of tumor virotherapy whereby replicating viruses are used as antitumor weapons. Replicating viruses seem to preferentially infect and multiply in tumor cells. The selective replication of the virus in tumor cells induces cell death with progeny virus infecting surrounding tumor cells leading to local viral amplification. Our work has focused on the use of a vaccine strain of measles virus that has potent and selective oncolytic activity against myeloma.⁶¹ Recently we have engineered a recombinant measles virus that induces expression of the thyroidal sodium iodide symporter (NIS) in tumor cells. These cells take up radioiodine allowing the non-invasive tracking of viral replication and gene expression in vivo. NIS expression also enhances the oncolytic effect of the virus by combining it with ¹³¹I that decays by the emission of electrons (beta particles) that induce cell death.⁶² This vector is expected to undergo clinical trials in the near future.

Conclusion

Within the last few years, there has been considerable progress in the understanding of myeloma biology. This is being translated into more effective and targeted therapies that can impact the disease as well as its environment in the bone marrow. These approaches, while not yet curative, provide better disease control and have improved the quality of life of patients with this illness.

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